OVARIAN NEW GROWTH IN PROGERIA

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ABSTRACT

The Hutchinson-Gilford progeria syndrome (HGPS) is a rare genetic disease that involves single-base gene mutation in the LMNA gene which results in the production of a dysfunctional and mutant lamin A protein called progerin. Progerin is found in increased concentration in normal older individuals hence patients present with phenotypic signs of aging. [1] Based on current studies, there is no established predisposition and association between abdominal masses, specifically ovarian masses in female, adolescent, progeria patients.

This is an adolescent female patient with progeria presenting with an ovarian mass. Further studies to establish the correlation between Hutchinson-Gilford progeria syndrome (HGPS) and abdominal masses specifically masses in the reproductive system have yet to be done. The exact mechanism by which progeria patients become predisposed to developing abdominal masses, specifically ovarian masses is still a grey area in research. Through this case report, routine abdominal ultrasound screening or routine abdominal CT scan can be done to screen for presence of masses in HGPS patients.

INTRODUCTION

The Hutchinson-Gilford Progeria Syndrome (HGPS) or progeria, is a sporadic autosomal dominant disease characterized by symptoms of premature aging. It is a rare genetic disease with an estimated incidence of 1 in 4 million live births and with a prevalence of 1 in 20 million living individuals. There is no known and reported gender, ethnic, or regional bias. [1] It affects both sexes and all races and is known to be present in approximately 40 different countries. According to Progeria Research Foundation, there are 20 recorded cases in North America, 16 cases in Central and Southern America, 16 cases in Central and Southern America, 24 cases in Europe and the Mediterranean regions, 4 cases in Africa, and 18 cases in Asia. [4] In the Philippines, the Philippine Pediatrics Society has no recorded case of Progeria since 2006.

HGPS is caused by a single-base gene mutation in the LMNA gene which results in the production of a dysfunctional and mutant lamin A protein called progerin. The lamin proteins are involved in crucial functions such as creating and maintaining the integrity of the nuclear scaffold, DNA replication, RNA transcription, organization of the nucleus, nuclear pore assembly, chromatin function, cell cycling, senescence, and apoptosis. Progerin is found in increased concentration in normal older individuals compared to younger individuals thus suggesting a role in normal aging. [1] The disease is characterized by its multi-systemic

affectation of the skin, bones, eyes, ears, kidneys, heart, brain, and reproductive development requiring a multidisciplinary approach in its diagnosis and management. Diagnosis has been standardized through a confirmatory genetic test of the LMNA mutation. [4]

While many systems are affected and involved in HGPS, normally functioning systems include the liver, kidneys, thyroid, immune system, gastrointestinal system, and neurological system. No intellectual delays were observed in progeria patients. [1] Aging phenotypes absent in HGPS include predisposition to forming masses, cancer, cataract, increased abdominal fat, and neurodegeneration. No studies and case reports available on online research databases has also presented a case of Progeria with an associated ovarian mass. Research has also shown that progeria patients are resistant to cancer due to the actions of BRD4 gene which inhibits tumorigenic potential of transformed cells. Furthermore, the mitochondrial dysfunction in HGPS leads to decreased ability to be dysplastic or anaplastic thereby making HGSP patients less likely to develop masses and have cancer. [2]

In addition to this, ovarian tumors in the pediatric age group are also not common. Ovarian tumor in the pediatric population has an estimated incidence of 2.6 cases per 100,000 girls per year. Furthermore, ovarian malignancy in children and adolescents is reported only in 10% to 20% of all ovarian masses or neoplasms and comprises approximately 1% to 2% of all childhood malignancies. [3] In a study conducted by Bhattacharyya et al., where they divided the cases into four age groups 1-5, 5-10, 11-15, and 16-20 years old, most of the ovarian tumors are seen in the age group of 16 to 20 years old (80%). [3] This is a report of a case of Progeria in a 14-year-old female with an ovarian mass. This paper will discuss the diagnostic approach and management of this rare phenotypic presentation of Progeria.

CASE REPORT

This is a case of a 14-year-old female who came in with a chief complaint of an ovarian mass. She is a known case of Hutchinson Gilford Progeria Syndrome who initially presented with prominent scalp veins at 6 months as noticed by the mother and was then diagnosed to have an LMNA gene mutation through a gene mutation test. Patient is currently being maintained on Lonafarnib (6mg/kg/day), a protein farnesyltransferase inhibitor (FTI) that inhibits progerin farnesylation, as part of a clinical trial. Patient has been enrolled in a clinical trial since 3 years of age and previously took pravastatin and zoledronate. Surveillance is done every other year since then and would include physical examination, bone scans, CT scans, and 2D echocardiography with Doppler. Last consultation was in 2019 and no consultation was done in 2021 due to the pandemic.

Six months prior to admission, patient was noted to have abdominal distension. The abdomen was increased by approximately 1/3 of the normal girth. This was not associated with a palpable mass, diarrhea,

vomiting, constipation, early satiety, bloatedness, or changes in frequency of bowel movement or in the caliber of the stools. No consultation was done, and no medications were taken. The mother claimed that the patient had occasional episodes of abdominal distention growing up. In the interim, there was persistence of the abdominal distension but there was no progression in size. No other associated symptoms were noted.

Two months prior to admission, the patient accidentally slipped and fell on her buttocks which resulted to a right hip dislocation. Patient then underwent closed reduction of the hip with traction. One month prior to admission, during a follow up consultation, a lateral hip CT scan revealed an incidental finding of ovarian mass which prompted further work up. At this time, patient still has abdominal distention that did not progress in terms of size, was associated with occasional bilateral lower quadrant sharp pain of the abdomen with pain severity of 4/10 for which patient has been taking paracetamol. There are no palpable masses, no changes in bowel movement and no urinary symptoms of increased frequency, urgency, and dysuria. A whole abdominal CT scan revealed a large unilocular cystic abdominopelvic mass lesion. Primary consideration was a bilateral ovarian serous cystadenoma.

Two weeks prior to admission, the patient still had persistent symptoms hence, she consulted a Pediatric gynecologist. CA-125, a marker of ovarian epithelial carcinomas was requested and revealed elevated results. Initial assessment was epithelial cell tumor carcinoma hence patient was advised surgery. Patient was then admitted after two weeks.

There are no other members of the family diagnosed with Progeria. There is, however, a family history of diabetes on the maternal side (maternal grandparents), and history of thyroid cancer on paternal side (paternal grandfather). There was no reported family history of ovarian masses and tumors, no hypertension, asthma, and other malignancies noted in the family. In terms of sexual and reproductive history, patient still has no thelarche and menarche.

COURSE IN THE WARDS

The patient was seen awake, conscious, and coherent with stable vital signs: blood pressure of 90/60, heart rate of 98, afebrile at 36.7 degrees Celsius, and O2 saturation at 99%. She is severely underweight and stunted with a weight of 13.5kg, Height of 101 cm ($z < -3$), and BMI of 13.1 ($z < -3$). Patient has dry skin and prominent scalp veins. She has alopecia, minimal subcutaneous fat, abnormal dentition, micrognathia, shrunken chin, and absence of eyebrows and eye lashes, there were no rashes or other skin lesions observed. She had anicteric sclerae with pink palpebral conjunctiva. Examination of the chest revealed symmetric chest expansion with no retractions and with clear breath sounds. She had an adynamic precordium with a normal heart rate, regular rhythm, and no murmurs. The point of maximal impulse was heard best at the fifth left intercostal space in the midclavicular line. There were no lifts, thrills, or heaves. The abdomen was globular

and distended with an abdominal circumference of 61cm, however, on palpation, it was nontender and no mass was palpated. On percussion, it was tympanitic on the upper quadrant with areas of dullness on the lower quadrants on percussion, with normoactive bowel sounds. She had grossly female genitalia with no pubic hair and had prepubertal breast buds (Tanner stage 1). The patient had limited range of motion of bilateral upper and lower extremities due to bilateral shoulder and hip dislocations. She had full and equal pulses, warm extremities, and capillary refill time less than 2 seconds with noted nail dystrophy. Neurological examination of the patient was unremarkable. Initial assessment on admission was ovarian new growth probably serous cystadenoma rule out epithelial cell carcinoma and patient is scheduled for and elective bilateral salpingo-oophorectomy with biopsy of suspicious lesions.

Patient underwent the planned procedure and tolerated the procedure well. Intraoperative findings showed a bilateral ovarian cystic mass with a smooth capsule and a normal looking uterus and fallopian tube. On cut section, the left ovary exuded serous fluid while the right ovary exuded seromucinous fluids. She was extubated immediately after the operation. There was also no bleeding on post-operative site. Patient was deemed stable and fit for discharge after 4th post-operative hospital day. The final pathologic diagnosis of the surgical specimens is bilateral ovarian serous cystadenoma with no significant pathologic changes (Figs. 1-4).

DISCUSSION

Ovarian mass in the pediatric population, specifically in patients who have not yet reached puberty, is uncommon with an estimated incidence of 2.6 cases per 100,000 girls per year. [3] In research conducted by Bhattacharyya et al. that studied 151 cases of ovarian tumors in the pediatric age group, the incidence of malignant ovarian tumors is 22.6%, while 78.4% of the ovarian tumors studied are benign. [3] Among the benign tumors, mature teratoma and serous cystadenoma are seen in all age groups. [3] They also divided the cases of ovarian masses in pediatric patients by age group (1-5, 5-10, 11-15, and 16-20 years old) and most of the ovarian tumors belonged to the age group 16 to 20 years old (80%). [3] In this case, we are presented with a middle adolescent 14-year-old female progeria patient with symptoms of an enlarging abdominal mass, which was incidentally detected on abdominal CT scan to be ovarian in origin.

Risk factors that predispose female patients to form ovarian masses include hormonal fluctuations, irregular menstruation, endometriosis, severe pelvic infections, family history of ovarian mass or cancer, and belonging to the reproductive age group with menarche, all of which are not present in this patient. The predisposition to form masses and cancer is one of the aging phenotypes absent in HGPS. They do not typically develop masses and cancer because they contain a tumor protection mechanism mediated by BRD4 (Bromodomain-containing protein 4). BRD4 inhibits abnormal growth of cells thus

inhibiting the oncogenic transformation of cells through its altered genome-wide binding patterns. [2] However, we are presented with a case of progeria with an ovarian mass.

In terms of sexual development, the patient has not yet reached her thelarche and menarche at 14 years of age and on physical examination the patient's stage of development can be classified as Tanner Stage 1 (prepubertal). Female progeria patients often have delayed sexual maturation and only develop until Tanner Stage II with signs of early breast development and sparse pubic hair. Only half of females with progeria achieve spontaneous menarche by age 14. [6] This pubertal delay is associated with the decrease in leptin levels in progeria patients due to the loss of subcutaneous fat that is important in leptin production. [6] Ovarian masses are also found to be less common in patients who have not yet reached menarche [2].

In this patient, CT scan of the whole abdomen (plain and with contrast) was done which revealed large unilocular cystic abdominopelvic mass lesions with thin capsules and with no ascites. Imaging features more suggestive of benign ovarian tumors include a mass with an entirely cystic component, thin wall (less than 3mm), lack of internal structure, and the absence of ascites. Malignant features in imaging studies include findings of thick and irregular walls, papillary projections, thick septa, and evidence of necrosis. [7] These were not seen in the imaging of the patient's abdomen hence the primary consideration based on the radiologic findings is a benign bilateral ovarian cystadenoma.

Another important laboratory test to further evaluate abdominal masses are tumor markers. In our patient, the tumor marker CA-125 was tested because she presented with an ovarian mass based on initial CT scan and CA-125 is known to be expressed by approximately 80% of ovarian epithelial carcinomas but less frequently by mucinous carcinomas. The marker is also increased in endometrial and tubal carcinoma, and in other malignancies such as those originating in the lung, breast, and pancreas. Our patient had elevated CA-125 results (96.88 U/mL) and this makes ovarian epithelial carcinoma a consideration as well.

The management of ovarian masses depends on the following factors: symptoms, size of the mass, age of the patient, medical history, and menopausal state of the patient. In most cases, unilateral salpingo-oophorectomy or ovarian cystectomy is an adequate treatment for ovarian masses. [8] In this patient, bilateral salpingo-oophorectomy was performed due to the presence of bilateral ovarian tumor. Important surgical considerations for our patient because she is a known case of progeria include difficult intubation because of the facial disproportion, narrowed nasal bridge, and retrognathia. Furthermore, progeria patients have a greater propensity for developing stroke under anesthesia due to the underlying stiffness of the blood vessels that make it challenging to maintain adequate blood pressure during general anesthesia.

The definitive diagnosis of ovarian masses is based on the histopathological examination of the surgical specimens: bilateral ovary and fallopian tubes. The final pathologic diagnoses of the surgical specimens are bilateral serous cystadenoma with no significant pathologic changes. Ovarian cysts are the most common adnexal mass in the pediatric population. [5] Ovarian tumors in the age group of 11-15 years old are mostly benign occurring in 60% of patients. The most common benign ovarian tumor in patients aged 11-15 years old is benign cystic teratoma occurring in 38% of the patients, this is followed by mucinous cystadenoma occurring in 30% of the patients, and lastly serous cystadenoma occurring in 23% of the patients. [3] Despite having an elevated level of tumor marker CA-125 which is a feature of a malignant lesion, patient still had a benign ovarian mass due to the enhanced activity of the BRD4 gene in Progeria which inhibits neoplastic transformation of cells.

Most serous cystadenomas are polyclonal, but monoclonal cystadenomas occur. These ovarian cystadenomas develop as a hyperplastic expansion from epithelial inclusions. [9] Serous cystadenomas are not associated with mutations in either KRAS or BRAF in contrast to serous borderline tumors and low-grade serous carcinoma. Macroscopic findings of serous cystadenoma ranges in size from 1 to more than 30 cm in greatest dimension. They have a smooth outer surface and contain one or more thin-walled cysts filled with clear, watery fluid. Serous cystadenomas are usually unilocular but may be multilocular. [9] In our patient, both ovaries have a smooth capsule with sizes ranging from 9 to 11 cm. On cut section, the left ovarian cyst exuded serous fluid while right ovary exuded seromucinous fluid. In addition to this, the histopathology of serous cystadenomas is composed of cysts and papillae lined by non-stratified or stratified cuboidal to columnar cells resembling fallopian tube epithelium, usually with no or minimal atypia. [9] In our patient, microscopic analysis of both ovaries revealed fragments of cysts lined by a single layer of flat to small cuboidal cells adherent to ovarian stroma with cysts line by an inner layer of granulosa cells and an outer layer of theca cells. No atypical and malignant cells were noted on both specimens (Figs. 1-4). In terms of immunohistochemistry, the immunohistochemical profile of serous cystadenoma is like that of normal ovarian surface epithelium and tubal epithelium. In addition to the positivity with most used epithelial markers, p63 is also positive in most cases. [9] Unfortunately, for this case, no immunohistochemical analysis was done.

As a progeria patient, certain organ systems involved in the disease must be properly screened and managed to limit complications of the disease. Other expected disabilities associated with the syndrome include multiple repeated hip and shoulder dislocations that may affect mobility, hearing loss, hyperopia, corneal ulceration, decreased visual acuity, stroke, and heart disease and subsequent failure. All these expected morbidities associated with progeria would require a multidisciplinary team approach in managing the patient as an outpatient.

The mean life expectancy of a patient with progeria is 13.4 years. [4] Approximately 80% of progeria deaths are caused by heart failure that can be precipitated by respiratory infection and by surgical intervention. Since progeria is a primary vasculopathy with increased vascular stiffening and with a propensity to form atherosclerotic plaques, common end-stage events include hypertension, angina, cardiomegaly, and congestive heart failure. [1] It is important to monitor the patient post-operatively because heart failure can develop following surgical intervention. Respiratory infection can precipitate heart failure hence it is important to avoid prolonged hospitalization of the patient to avoid hospital acquired pneumonia. At this time of the COVID pandemic where the viral disease is still rampant and is highly contagious, it is important to educate the patient, as well as other household members, to always practice social distancing, wear proper protective equipment, and practice adequate personal hygiene. Through these preventive measures, the patient can be protected from getting the disease and consequently avoid having severe respiratory infections.

Anticipatory guidelines include strict fall precaution and avoidance of strenuous activities that may put the patient at risk of head trauma and skeletal injuries that may lead to recurring hip and shoulder dislocations. Anticipatory guidelines for adolescent patients, such as our patient, include self-breast examination, healthy lifestyle through physical activity that is appropriate for the patient, proper diet, avoidance of alcohol, smoking, and drug use, counseling on sexual behavior and risk of acquiring STIs, injury and accident prevention strategies such as use of sports protective gears, use of seatbelts, no driving under the influence of alcohol, and no handgun use. [10] It is also important to complete the immunization of the patient by administering the following vaccines that must be given to adolescent patients: influenza vaccine annually, HPV vaccine (3 doses following the 0, 1-2, and 6-month schedule), and PCV vaccine (1 dose of PCV 13 and 1 dose of PCV 23).

Having a child diagnosed with progeria has a major impact on the family hence genetic counseling must be done to the family as well. HGPS is a sporadic autosomal dominant disease which means that it follows an autosomal dominant inheritance wherein the condition can be passed down from a diagnosed progeria parent to her offspring. One copy of the mutated gene from one parent can cause the genetic condition. For healthy parents who already have a child with progeria, the chance of having another affected child is much higher at about 2-3%. This is due to genetic mosaicism where a parent's gene has the genetic mutation for progeria in a small proportion of their cells, but they do not manifest the disease phenotypically. [11] In this case, the family of the patient underwent genetic counseling and the prognosis of the disease as well as the probability of having another child with progeria was adequately explained to them as well.

The patient recovered well from the operation with no complications. She is now being optimized again to undergo surgical

repair of her bilateral shoulder dislocation so she can regain full functionality and mobility.

SUMMARY

The Hutchinson-Gilford progeria syndrome (HGPS) is a rare genetic condition that requires a multidisciplinary approach in management. This case presents an adolescent female patient with progeria presenting with an ovarian mass. Further studies to establish the correlation between Hutchinson-Gilford progeria syndrome (HGPS) and abdominal masses, specifically masses in the reproductive system have yet to be done. Routine abdominal ultrasound screening or routine abdominal CT scan can be done to detect presence of masses in HGPS patients. Female adolescent patients diagnosed with progeria should also be routinely seen and examined by a pediatric gynecologist for further evaluation of possible reproductive pathologies and delayed sexual development.

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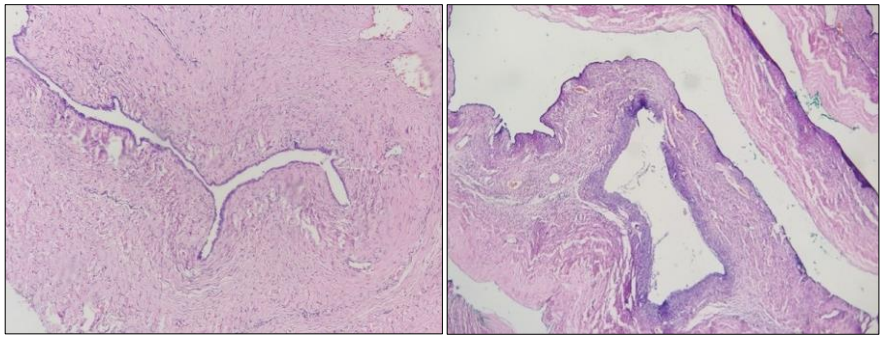

Figure 1. Left Ovary, LPO

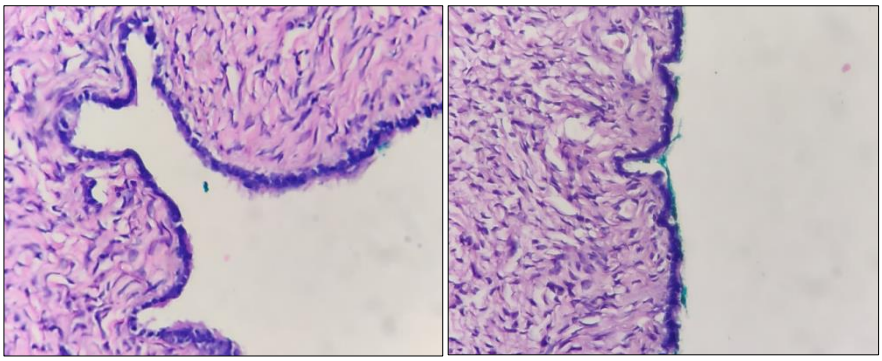

Figure 2. Left ovary, HPO

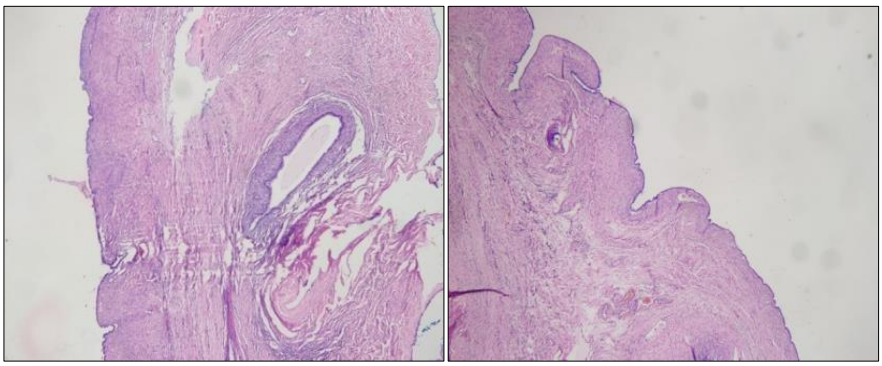

Figure 3. Right ovary, LPO

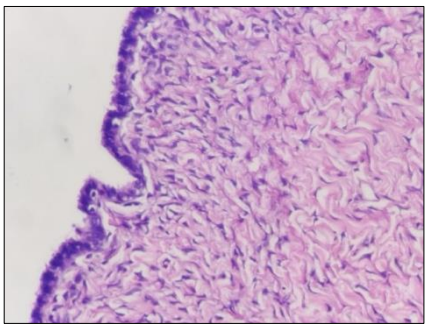

Figure 4. Right ovary, HPO