Familial Thoracic Endometriosis Syndrome: case report

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Disclosure: None

ABSTRACT

Background: The presence of functional endometrial tissue in the tracheobronchial tree, pleura, and lung is normally referred to as thoracic endometriosis (TE) or extra genital endometriosis. The commonest extragenital site of endometriosis is within the thoracic cavity. The association of catamenial pneumothorax, catamenial haemorrhagic pleural effusion (haemothorax), catamenial haemoptysis and pulmonary nodules is referred to as thoracic endometriosis syndrome. The same mechanism of inheritance of genital endometriosis applies to extragenital endometriosis. No such report has been described in South-South, Nigeria.

Case summaries:

Case1. We present EA, a 26-year-old chef/baker who presented to our unit on account of recurrent cyclical right sided chest pain and difficulty in breathing, recurrent haemoptysis and cyclical abdominal pain and swelling with multiple tender umbilical nodules. On examination she was found to be in respiratory distress but not cyanosed, with SPO2 of 97-99% on room air. Examination of the chest revealed a right sided chest fullness and reduced movement with breathing. Percussion note was stony dull and absent breath sounds on the right hemithorax. Abdominal examination revealed a moderately distended abdomen with positive fluid thrill. Both pleurocentesis and paracentesis abdominis yielded an acellular haemorrhagic fluid; and pleural and lung biopsy demonstrated endometrial stroma and gland. Imaging examination by way of chest X-ray showed a homogenous opacity of the right hemithorax and a pulmonary nodule following drainage. A diagnosis of Thoracic Endometriosis Syndrome was made. She had VATS with lung and pleural biopsy, pleural abrasion and a closed thoracostomy tube drainage.

Case 2. We present JA a 29-year-old lady, a filling station attendant who presented to our unit with a history of gradual onset of right sided chest pain, progressive difficulty in breathing, non-productive cough, and abdominal pain and swelling. On examination she was found to be in respiratory distress but not cyanosed, with SPO2 of 98% on room air. Examination of the chest revealed a right apical flattening, reduced ipsilateral chest movement with breathing. Percussion note was stony dull and absent air entry on the ipsilateral hemithorax. Abdominal examination showed a mildly distended abdomen with a positive shifting

dullness. Both pleurocentesis and paracentesis abdominis yielded a haemorrhagic fluid acellular and pleural and lung biopsy demonstrated endometrial stroma and gland. Imaging examination by way of chest X-ray showed a homogenous opacity of the right hemithorax. A diagnosis of Familial Thoracic Endometriosis Syndrome was made. She had USS guided lung and pleural biopsy and a closed thoracostomy tube drainage. She had chemical pleurodesis with tetracycline.
Conclusion: Familial thoracic endometriosis syndrome is the diagnosis in a lady of reproductive age whose sibling had earlier presented with cyclic or acyclical recurrent right sided chest pain, cyclical or acyclical dyspnoea, haemoptysis, cyclical or acyclical abdominal swelling and peritonitis.

INTRODUCTION

The presence of functional endometrial tissue in the tracheobronchial tree, pleura and lung is referred to as thoracic endometriosis (TE) or extra genital endometriosis[1,2]. The most common extragenital site of endometriosis is within the thoracic cavity [3]. The association of catamenial pneumothorax, catamenial haemorrhagic pleural effusion (haemothorax), catamenial haemoptysis and catamenial pulmonary nodules is referred to as thoracic endometriosis syndrome (TES)[4]. Thoracic endometriosis was described in the early twentieth century by Di Palo S et al (they were the first) as endometriosis causing pulmonary lesions consisting of endometrial glands and stroma. Endometriosis is a disease in women of child bearing age[5], however, endometriosis has been reported in men and postmenopausal women on prolonged estrogen[6]. While the peak incidence of TES has been reported to occur between 30-35years (which is a decade later than the genital endometriosis[7]), our patients are two biological sisters of the same parents aged 26years and 29years respectively. Again, while the elder sister presented with symptoms at the age of 26years, the younger sister presented to us with symptoms at the age of 29years. This was not a mere coincidence. Both are young single educated ladies. The elder is a professional cake baker and chef and the younger is a filling station attendant. Since both are single, infertility for now is not a problem but both are aware that pregnancy slows down its progression. However, chances of conception are reduced because of chronic inflammation and fibrosis. The problem is the recurrent symptoms, frequent outpatient clinic visits and the high cost of medical management of this disease. While the elder had VATS with pleural biopsy and lung biopsy and pleural abrasion with subsequent fusion of the pleurae after thoracic catheter drainage and adequate lung expansion. The younger could not afford VATS procedure but rather had placement of a thoracic catheter for drainage and subsequent trucut pleural and lung biopsy. She had chemical pleurodesis using tetracycline, lignocaine and normal saline after complete drainage with adequate lung re-expansion as inadequate drainage and inadequate lung re-expansion are two independent risk factors in recurrent catamenial haemorrhagic effusion (haemothorax). The symptoms of the elder (Case-1) started at the age of 26 years with cyclical right sided chest pain, cyclical difficulty in breathing, cyclical abdominal swelling and discomfort, painful umbilical

nodules, non-productive cough and cyclical haemoptysis. The younger sister (Case 2.) started three years later at age of 29 years. From our knowledge of the disease, we expected a more fulminant course and with a background family history of the disease, as more proactive measures were taken in managing her disease.

Patient's characteristics are showed in table 1.

Lung and pleural biopsies demonstrated both endometrial stroma and glands as shown in Fig 2.

CASE REPORT

CASE 1: Miss E A. A 32-year-old chef presented to us via Accident and Emergency with a history of recurrent cyclical right sided chest pain, recurrent cyclical difficulty in breathing, recurrent cyclical generalized abdominal pain and recurrent cyclical abdominal swelling with severe umbilical tenderness. There was no history of chronic cough nor contact with anyone with chronic cough. There was an episode of haemoptysis which began a week before her menses lasting for nearly three weeks, without a history of fever or weight loss.

Examination showed a young lady in severe respiratory distress with respiratory rate of 32cycles per minute, peripheral capillary oxygen saturation (SPO_2) 97-99% at room air. She was not pale, not dehydrated with no significant peripheral lymph nodes enlargement. Blood Pressure was 110/70mmHg, pulse rate was 82b/min. Percussion note was stony dull with absent air entry on the right hemithorax. The abdomen was mildly distended, moved with respiration, there were multiple tender umbilical nodules and fluid thrill was positive. The digital rectal examination was essentially normal. Both pleurocentesis and paracentesis abdominis yielded haemorrhagic fluid both of which were acellular at cytology. The Pre-Video Assisted Thoracoscopic Surgery (VATS) chest X-ray showed homogenous opacity of the right hemithorax. She had VATS with pleural and lung biopsy, then mechanical pleural abrasion with eventual fusion of the pleurae.

Case 2: Miss J A. is a 29-year-old lady, a filling station attendant who presented to us via Accident and Emergency with a history of gradual onset of right sided chest pain, severe at outset and later mild and continuous made worse with lifting heavy objects. This was associated with progressive difficulty in breathing, initially after a whole day work but recently by walking from one pump to another and subsided with rest. There was an associated non-productive cough. There was no personal history of chronic cough nor contact with anyone with chronic cough and no haemoptysis. She noticed a gradual onset of generalized abdominal discomfort and swelling. There was no history of fever or weight loss.

Examination showed a young lady in severe respiratory distress with respiratory rate of 36cycles per minute, she was not pale, not cyanosed and was not dehydrated. Blood Pressure was 110/70mmHg, pulse rate was 84b/min and peripheral oxygen capillary saturation was 98 % on room air. Chest examination showed a reduced right sided chest movement with respiration, there was an associated stony dull percussion note and absent air entry on the right hemithorax. The abdomen was mildly distended,

moved with respiration, and with a positive shifting dullness. The digital rectal examination was essentially normal. Both pleurocentesis and paracentesis abdominis yielded haemorrhagic fluid both of which were acellular at cytology. The Pre closed thoracostomy tube drainage chest X-ray showed homogenous opacity of the right hemithorax. The Full blood count was within normal range, the erythrocyte sedimentary rate was within the normal range. Both acid and alcoholic-fast bacilli and GeneXpert were negative for tuberculosis. A trucut pleural and lung biopsy demonstrated endometrial gland and stroma. She had closed thoracostomy tube drainage with full lung expansion and chemical pleurodesis with a solution of tetracycline was used to obliterate the pleural cavity.

Conclusion:

Familial thoracic endometriosis syndrome is the diagnosis in a lady of reproductive age whose sibling had earlier presented with cyclic or acyclical recurrent right sided chest pain, cyclical or acyclical dyspnoea, haemoptysis, cyclical or acyclical abdominal swelling and peritonitis.

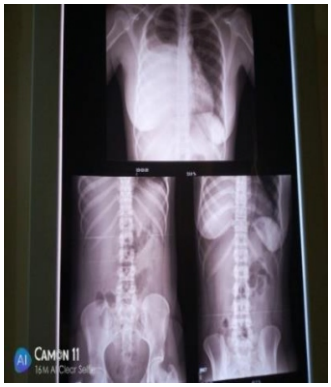

Fig 1. Pre-VATS, lung and pleural biopsy and drainage (Case1)

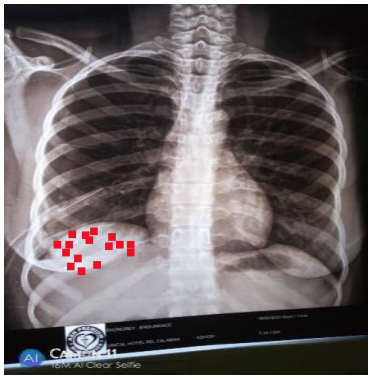

FIG 2. Post drainage chest X-ray (case 1)

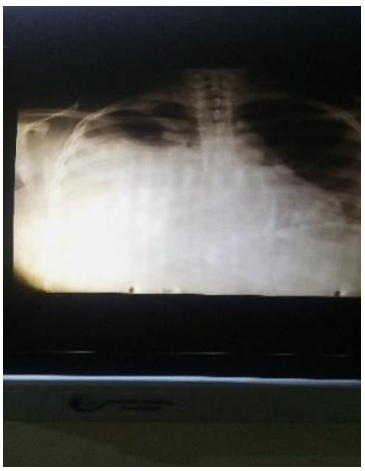

FIG 3. Pre-drainage and USS guided pleural and lung biopsy chest X-ray (Case 2)

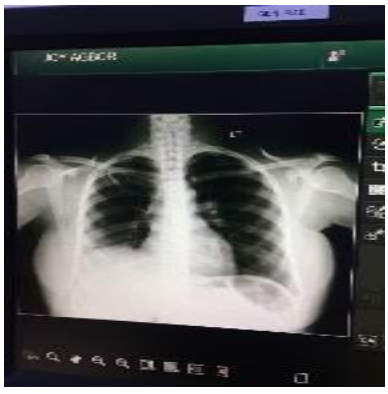

FIG 4. Post-drainage, Chest X-ray (Case 2)

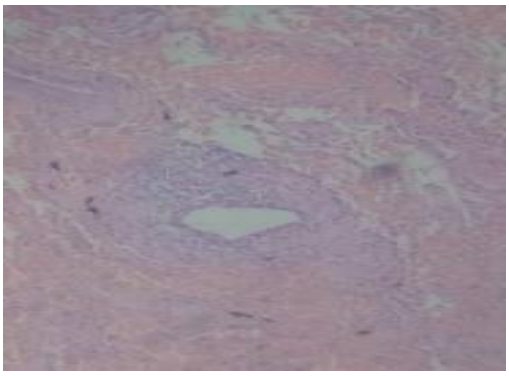

FIG 5(case1)

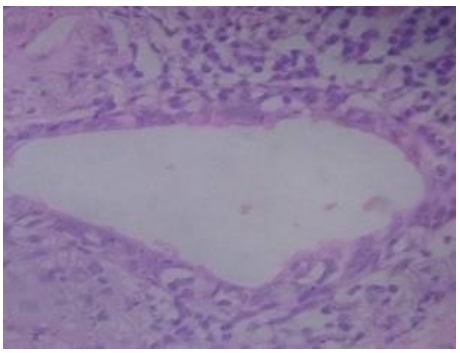

FIG 6(case 2). Both histology showed endometrial glands and stroma

DISCUSSION

Endometriosis is clearly heritable, but the precise mechanism or mechanisms remain unclear. The magnitude of the increased risk (5% to 8% of first-degree relatives) is more reminiscent of polygenic/multifactorial tendencies than a single mutant gene.

However, this recurrence risk is higher than the 2% to 5% expected risk for polygenic inheritance. The frequency of affected relatives might even be higher if one could directly measure a gene product or products. Although Mendelian mechanisms cannot be excluded, polygenic inheritance seems more likely if one assumes all endometriosis, is a single disorder. If it is, the increased severity in familial cases is also consistent with predictions based on a polygenic model. Such a model predicts that the greater the severity, the greater the underlying genetic liability and, hence, the greater the proportion of affected relatives. Endometriosis was more severe in familial cases, which also lessens the likelihood that the presence of an affected family member led to the identification of an affected relative merely because of a higher index of clinical suspicion.

The other formal explanation, and perhaps the most likely (*i.e.*, not all endometriosis is the same disorder), is genetic heterogeneity. One or more forms of endometriosis might be Mendelian despite the larger proportion being nongenetic or polygenic. This has proved to be the likely explanation for peptic ulcer and other adult-onset disorders. Study by Ishii K et al showed an association between HLA - DQB1 and HLA-DPB1 and endometriosis, which is more suggestive. The evidence for an association between genetic polymorphisms and risk of endometriosis is robust[8]

Endometriosis is a complex disease with multiple genetic and environmental factors contributing to the disease pathology[9,10]. The first evidence for the presence of a heritable component contributing to endometriosis came from studies published as early as twentieth century[6] that demonstrated familial clustering of endometriosis[8,11]. These studies showed that the first-degree relatives of affected women have a five to seven times higher risk of being diagnosed with endometriosis[8,11] Familial endometriosis was further shown to be associated with earlier age of symptom onset and a more severe disease course[8] The genetic predisposition to endometriosis was corroborated by a twin

study that showed an increased disease risk in monozygotic versus dizygotic twins and the estimated contribution of genetic factors to endometriosis was up to 51%[8].

Large scale genetic linkage and meta-analysis represented an important means to identify endometriosis susceptibility loci[8]. Most notably, family-based linkage studies of endometriosis conducted by the International Endogene Consortium in a two combined cohort studies of Australian and United Kingdom families identified linkage regions that likely habour rare casual endometriosis variants, one on Chromosome 10q26[8] and one on Chromosome 7p13-15[8].

A third region suggestive of linkage identified by Treloar et al is located on Chromosome 20p13[8] · Chromosome 10q26 contains two genes that were previously implicated in candidate gene mapping studies as potential risk loci EXMX2[8] which encodes a transcription factor required for reproductive tract development[10,] and the tumour suppressor gene PTEN which encodes a phosphatidylinositol-3,4,5 triphosphate-3-phosphatase[12]

Both EXMX2 and PTEN were previously reported to be aberrantly expressed in endometrial lesions[8] However, systematic resequencing of the region could not confirm either genos as an endometriosis risk locus[8] instead, CYP2C19 (Cytochrome P450 family of subfamily (member19), a nearby gene was found to be weakly associated with endometriosis[8]. CYP2C19 is a member of the cytochrome P450 family and encodes an aromatase associated with the metabolism of drugs and estrogen[8]. The linkage peak on Chromosome 7p13-15 may represent a susceptibility allele with a high penetrance for a more severe form of endometriosis[8] but the involved allele remains elusive.

Table 1. Showing Patient's characteristics

PATIENT'S CHARACTERISTICS	**CASE 1**	**CASE 2**	**REMARK**
Sex	**Female**	**Female**	**100%**
Age	29years	31years	
Age At Presentation	26years	29years	100%
Cyclical/Acyclical Right Sided Chest Pain	Yes	Yes	100%
Cyclical/Acyclical Difficulty In Breathing	Yes	Yes	100%
Cyclical /Acyclical Cough	Yes	Yes	100%
Cyclical/Acyclical Haemoptysis	Yes	No	50%
Cyclical/Acyclical Abdominal Swelling/Peritonitis	Yes	Yes	100%
Peritonitis	Yes	Yes	100%
Pulmonary Nodule	Yes	No	50%
Medical Treatment	Yes	No	50%
Laparoscopy	Yes	No	50%
Video Assisted Thoracoscopy	Yes	No	50%
Closed Thoracostomy Tube Drainage	Yes	Yes	100%
Histological Diagnosis	Yes	Yes	100%
Full Blood Count	Normal	Normal	100%
Esr	Normal	Normal	100%
Pleural Acid/Alcohol Fast Bacilli	Negative	Negative	100%
Genexpert	No MTB detected	No MTB detected	100%

Other genome-wide association studies in women in European ancestry led to the identification of two new genomic regions associated with a significant risk of endometriosis. The first locus with significant disease association is located to Chromosome 7p15.2[8]. This region may regulate expression levels of nearby gene(s) involved in the development of uterus and endometrium[8]. A second genetic variant was mapped to chromosome 1p36 near the WNT4 gene[8], which is implicated in the development and function of the female reproductive tract and sex hormone metabolism. Both loci were independently confirmed in Japanese and European cohorts[8].

Genome wide-studies identified additional susceptibility loci for endometriosis[8,13,14] several candidate genes were mapped that exhibit varying degree of disease association including gene involved in hormone signaling (GREB1) cell proliferation (ID4, CDKN2PAS), as well as cell migration and invasion (FN1, VEZT)[8]. However, most polymorphisms identified by genome-wide association studies to date are located in non-coding regions, suggesting they affect the expression of nearby genes.[8]

Genome-wide association studies with few exceptions, failed to confirm a clear association between endometriosis and specific risk loci. This may indicate that there are many genetic variants, each of which has a weak impact on endometriosis development, yet in combination they can significantly increase the likelihood of endometriosis and thus, represent true endometriosis risk loci[8,15]. Detection of weak effects of gene variants influencing a complex trait such as endometriosis, therefore, require datasets of significant size.

CONCLUSION

Thoracic Endometriosis Syndrome is a familial disease like our patients born of the same parents. There are no ongoing gene studies to unravel how this disease is inherited among the Black race of African descents. But we know the that the mode of inheritance may be similar to that of the Caucasians.

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