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Developmental Environmental Exposure Alters the Epigenetic Features of Myometrial Stem Cells

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THE BIOLOGY OF UTERINE FIBROIDS

Uterine fibroids (UFs), are the most common pelvic tumors, occurring in 70-80% of all reproductive-aged women and are the leading indication for hysterectomy worldwide. Although UFs are benign tumors, they typically cause severe menstrual bleeding, pelvic pain, preterm labor, recurrent abortion, and infertility. Hysterectomy is currently the main treatment used in women who no longer desire childbearing. UFs are hormonally responsive to estradiol and progesterone as well as other steroid hormones, and regress after menopause.

THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

The Developmental Origins of Health and Disease (DOHaD) paradigm is one of the most rapidly growing areas of biomedical research now-a-days. This research field originated with early findings that prenatal nutrition was linked with late-onset coronary heart disease and malnutrition and low-level exposures to drugs and toxic substances are well tolerated by a pregnant woman, but her gestating fetus would be afflicted by adverse effects, some of which might become obvious only later in life. The field has now broadened to encompass a variety of environmental and occupational hazards. When these environmental insults disrupt early developmental processes, they may cause permanent changes in cellular characteristics that persist and then lead to increased susceptibility to a variety of diseases later in life.

Unlike in the adult, the perinatal/neonatal organ’s response to environmental exposure is much more rapid and severe. Environmental exposure is capable of causing organism toxicity due to immature immune system, lack of deoxyribonucleic acid (DNA) repair, poor liver metabolism, and incompletely formed organ barriers in early life stage. In addition to toxicity, environmental exposures during critical periods of organ development can permanently reprogram normal physiological responses to increase susceptibility to diseases later in life. The epigenomic programming that occurs during development exhibits a high degree of plasticity, and is modifiable by extrinsic factors such as environmental exposures.

MOLECULAR MECHANISM OF REPROGRAMMING: ENVIRONMENTAL FACTORS ALTERS THE EPIGENOME OF UTERUS

Due to the plasticity during development of tissues and organs including uterine, accumulating evidence has shown that environmental factors act on epigenome via DNA methylation and histone modification, which eventually lead to alteration of gene expression pattern and related diseases later in life. In utero the exposure of bisphenol A (BPA), an organic synthetic compound belonging to the group of diphenylmethane derivatives and bisphenols, altered the global CpG methylation profile of the uterine genome and subsequent gene expression pattern. Changes in estrogen response were accompanied by altered methylation that preferentially affected estrogen receptor-α (ERα)-binding genes. Neonatal exposure of CD-1 mice to dieth-
ystilbestról (DES), a synthetic non-steroidal estrogen of the stilbestrol group, induced uterine adenocarcinoma in aging animals, concomitantly decreasing DNA methylation of nucleosome binding protein 1 (Nsbp1) promoter CpG Island (CGI) in the uteri which leads to persistent overexpression of Nsbp1 throughout life. Moreover, 17β-estradiol and other environmental estrogens (DES and genistein) are capable of inducing phosphoinositide 3-kinase (PI3K)/AKT non-genomic estrogen receptor signaling to the histone EZH2, and therefore reduced levels of trimethylation of lysine 27 on histone H3 in hormone-responsive cells. These studies provide a direct link between xenoestrogen-induced nuclear hormone receptor signaling and modulating of epigenetic machinery in response to environmental estrogen in UFs.

**EPIGENETIC REPROGRAMMING OF STEM CELLS IN UTERINE FIBROIDS IN RESPONSE TO EARLY-LIFE EXPOSURES TO ENDOCRINE DISRUPTING CHEMICALS**

For environmental diseases, a central subject to resolve is the role of stem cells in the tumorigenesis or pre-cursors of degenerative diseases. Developmental adverse exposures may affect the highly regulated differentiation of hematopoietic stem cells, and even slight changes in the feature of these cells may serve as indications of health effects that may not be observed until later in life and may be magnified during the entire life. The environmental exposure directs the behavior of stem and progenitor cells, the fundamental source from which all tissues derive. However, environmental health studies are lacking on stem cells. UF growth and progression depend on a specialized subpopulation of tumor cells, termed tumor initiating cells (TICs). Thus, TICs represent a critical therapeutic target, but the molecular mechanisms that regulate them are poorly understood.

To determine the mechanism underlying increased risk of UF development at stem cell levels, we have recently determined the effect of early-life exposure to endocrine disrupting chemicals (EDCs) on stem cell behavior as well as characterized myometrial stem cells (MSCs) as a target for ethnic and environmental factors that increase UF risk. We utilized Eker rats carrying a germ-line mutation in the tuberous sclerosis complex 2 (Tsc2) tumor suppressor gene, that are susceptible for development of UFs which share similar anatomic, histologic, and biologic features to human UFs. Using this model, we isolated and characterized Stro1+/CD44+ MSC/progenitor-like cells that give rise to UFs, which resides in the rat cervix, a hypoxic niche in the uterus. These Stro1+/CD44+ MSCs responded to environmental cues, and expanded in response to developmental environmental exposures that promote UF development.

Human female reproductive tract has been shown to be a target for developmental programming as a result of inappropriate early life hormone exposure. Early life exposure to EDC compounds have been connected to increased risk of adult onset of UFs in women. Minority communities are particularly at risk for hazardous environmental exposures. However, similar inquiries in humans are lacking due to difficulties in collecting suitable human myometrial samples and/or to ascertain environmental exposures. We proposed that myometrium from a non-fibroid uterus that does not exhibit any detectable myometrial pathology (removed in humans are lacking due to difficulties in collecting suitable human myometrial samples and/or to ascertain environmental exposures).

To determine the mechanism underlying increased risk of UF development at stem cell levels, we have recently determined the effect of early-life exposure to endocrine disrupting chemicals (EDCs) on stem cell behavior as well as characterized myometrial stem cells (MSCs) as a target for ethnic and environmental factors that increase UF risk. We utilized Eker rats carrying a germ-line mutation in the tuberous sclerosis complex 2 (Tsc2) tumor suppressor gene, that are susceptible for development of UFs which share similar anatomic, histologic, and biologic features to human UFs. Using this model, we isolated and characterized Stro1+/CD44+ MSC/progenitor-like cells that give rise to UFs, which resides in the rat cervix, a hypoxic niche in the uterus. These Stro1+/CD44+ MSCs responded to environmental cues, and expanded in response to developmental environmental exposures that promote UF development.

Although the role of MSCs in development of UFs is extremely important, the molecular mechanism underlying developmental exposure to EDCs and other toxins at MSCs levels has not been characterized before. By ribonucleic acid (RNA)-sequencing analysis, we recently identified some key genes including estrogen responsive genes (ERGs) that are differentially regulated in MSCs early-life exposed to diethylstilbestrol (DES) versus control (VEH). Subsequently, we performed gene set enrichment analysis on the ChiP-sequencing data and found enrichment of histone H3 trimethylated at lysine 4 (H3K4me3) (an active mark for gene transcription) at the promoters of ERGs in DES-MSCs as compared to VEH-MSCs. Furthermore, the increased expression of ERGs in DES-MSCs was positively correlated with the elevated H3K4me3 epigenetic mark. Our current study suggest that early life exposure to DES during sensitive periods of uterine development increases the risk of UF development by reprogramming the epigenome of MSCs towards a pro-fibroid epigenomic landscape. Further understandings of EDC-induced epigenetic alteration and DNA mutations in MSCs have the potential to substantially advance UF research.

**ACKNOWLEDGEMENTS**

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CONFLICTS OF INTEREST

None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

REFERENCES


22. Laiosa MD, Tate ER. Fetal hematopoietic stem cells are the canaries in the coal mine that portend later life immune deficiency. *Endocrinology.* 2015; 156: 3458-3465. doi: 10.1210/en.2015-1347


Case Report

Cryptococcal Meningitis in Pregnancy, the Neglected Diagnosis: A Case Report

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ABSTRACT

Introduction: Cryptococcal meningitis is an opportunistic infection of human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) that can cause maternal and fetal mortality and morbidity. This case report aims to help clinicians to consider it as a differential diagnosis in HIV-seropositive pregnant women presenting with vague symptoms. This is particularly important as HIV/AIDS is now a global pandemic. There is a test available for disease surveillance.

Case Report: A 31-year-old P3 G4 HIV seropositive patient on antiretroviral therapy/cotrimoxazole presented at 29 weeks gestation by dates complaining of draining clear fluid per vagina for 24 hours, slight frontal headache and vomiting. On admission, she was ill-looking but was afebrile with a body temperature of 36.2 °C. A sterile speculum examination confirmed ruptured membranes with a pool of liquor in the posterior vaginal fornix. She was treated as a case of preterm pre-labour rupture of membranes. Therapy consisted of erythromycin and dexamethasone. She complained of increasing frontal headaches and vomiting and on detailed examination was found to be now having neck stiffness. A lumbar puncture was performed and microscopy showed Cryptococcus neoformans. She was managed by a multidisciplinary team involving physicians and was treated with antifungals. She delivered prematurely by normal vaginal delivery a baby boy weighing 2100 g with Apgar 7 and 9 scores at 1 and 5 minutes respectively. Post-partum she continued to fit for a day but subsequently the convulsions stopped and the patient began to improve clinically.

Conclusion: There is need to raise awareness amongst clinicians about serious opportunistic infections in HIV infected pregnant mothers for early diagnosis and treatment. Antifungal therapy can be life-saving and prevent maternal deaths.

KEYWORDS: Cryptococcal meningitis; Pregnancy; Amphotericin B; Maternal death; Perinatal outcomes.

INTRODUCTION

The first cases of Cryptococcal neoformans meningitis in pregnancy in the literature were described in 1962 and 1972. It is an opportunistic fungal infection that presents with an insidious onset. Fungal spores like those in Figure 1 can be found in the cerebrospinal fluid in the brain causing significant maternal morbidity and mortality. There is currently sparse information on this subject in the literature. Cryptococcal meningitis is a serious disease that can cause adverse maternal and fetal outcomes especially in HIV/AIDS infected patients. Furthermore, pregnancy is immunosuppressive hence the combination with HIV can be catastrophic with maternal death. The disease can occur in HIV sero-negative and sero-positive patients. The HIV/AIDS pandemic has assumed global status and the cases that occur need to be reported to raise clinical awareness. Awareness among clinicians is vital to help with early diagnosis, treatment and reduce morbidity and mortality.
CASE REPORT

A 31-year-old P3 G4 HIV seropositive patient on antiretroviral therapy/cotrimoxazole presented at 29 weeks gestation by dates complaining of draining clear fluid per vagina for 24 hours. She also complained of a slight frontal headache and vomiting. She had been feeling dizzy and having generalised body weakness for the past 2 months.

On admission, she was ill-looking but was afebrile with a body temperature of 36.2 °C. Her blood pressure (BP) recording was 122/76 mmHg. The fetal heart was normal on Pinard auscultation. A sterile speculum examination confirmed ruptured membranes with a pool of liquor in the posterior vaginal fornix. A high vaginal swab was taken.

The differential diagnosis was that of preterm pre-labour rupture of membranes and urinary tract infection. A full blood count showed a normocytic normochromic anaemia of 9.8 g/dl, white blood cell (WBC) count of 10.63×10⁹/L, a platelet count of 297×10⁹/L. The CD4 count was 379 cells/mm³. Urinalysis showed no glucosuria and a trace of protein and a sample was sent for microscopy and culture. An ultrasound scan showed a fetus of 30 weeks gestation and adequate liquor volume. Therapy consisted of Erythromycin 250 mg 6 hourly per os to prevent infections and dexamethasone 6 mg intramuscularly twice per day for 2 days for fetal lung maturation. The high vaginal swab and urine samples did not grow any organisms on culture.

After 3 days of admission, she complained of increasing frontal headaches and vomiting. The blood pressures remained within normal ranges. On detailed examination she was found to be now having neck stiffness. A lumbar puncture was done. The cerebrospinal fluid (CSF) was clear but under pressure. CSF glucose and proteins were normal. Microscopic examination showed Cryptococcus neoformans. The culture also grew Cryptococcus neoformans. The serum cryptococcal antigen (CrAg) test was positive.

A team of physicians was consulted and reviewed the patient. The patient was commenced on Amphotericin B 50 mg intravenously once daily plus Fluconazole 800 mg once daily per os. She received dexamethasone 10 mg intravenously 8 hourly.

After 3 weeks of therapy she started having convulsions. The patient went into preterm labour and delivered by normal vaginal delivery a baby boy weighing 2100 g with Apgar scores 7 and 9 at 1 and 5 minutes respectively. Post-partum she continued to fit for a day but subsequently the convulsions stopped and the patient began to improve clinically. A fortnight after delivery she was completely fit free and asymptomatic and able to sit up and feed properly. The neonate was well, needing no further treatments.

DISCUSSION

This case report is important in that it raises awareness about an important condition that may cause considerable morbidity and mortality in pregnant patients. Other studies and case reports have reported similar clinical scenarios. This case report therefore adds more knowledge about this condition. Increased awareness can help reduce poor perinatal outcomes.

The differential diagnosis in this patient included pre-eclampsia/eclampsia but there was no clinical or laboratory evidence to support this diagnosis as the patient had no proteinuria or elevated blood pressures. The other diagnosis to consider was tuberculous meningitis (TBM) but the lumbar puncture results were conclusive for cryptococcal meningitis (CM). HIV/AIDS presentation can present with abnormal ways such as opportunistic infections like cryptococcal meningitis.

The prevention of cryptococcal meningitis in subclinical cases in HIV infected patients with CD4 cell counts of <100 cells/mm³ is possible. The diagnostic use of cryptococcal capsular polysaccharide antigen (CrAg) in serum is advisable this allows life-saving antifungal therapy to be initiated. In low resource settings, this test is not readily available due to cost implications. In the presented case there was delay in diagnosis as
there were vague clinical symptoms pointing to a serious condition such as meningitis.

The management of the patient should be multidisciplinary involving physicians. Antifungal chemotherapeutic drugs used include Amphotericin B alone or in combination with fluconazole. Fetal teratogenic effects of these drugs have not been reported, in fact both good maternal and fetal outcomes have been reported. Another antifungal drug that can be used is fluconazole or itraconazole with good outcomes.

Cryptococcal placental infection without neonatal infection has been reported in the literature. Only one case of mother-to-child transmission of cryptococcosis has been described in the literature. In this case report, the baby did not seem any signs of being affected hence did not need any further treatments. Patients followed up to 8 months post-infection have shown no signs of infection.

CONCLUSION

There is need to raise awareness amongst clinicians about serious opportunistic infections in HIV infected pregnant mothers for early diagnosis and treatment. The widespread use of CrAg as a screening tool can help early disease detection hence allowing the commencement of antifungal therapy that can be life-saving and prevent maternal deaths.

CONSENT

The authors obtained written informed consent from the patient for submission of this manuscript for publication.

REFERENCES


5. Vidal JE, Boulware DR. Lateral flow assay for cryptococcal antigen: An important advance to improve the continuum of HIV care and reduce cryptococcal meningitis-related mortality.


A Series of Rare Chronic Histiocytic Intervillositis Cases and its Association With Fetal Growth Restriction

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ABSTRACT

Objective: To re-evaluate a series of 6 diagnosed cases of chronic histiocytic intervillositis (CHI) its relation to recurrent pregnancy losses, and fetal growth restriction (FGR).

Methods: A retrospective study was conducted where patients were identified from the Department of Obstetrics and Gynecology database in Sant Joan de Deu Hospital (HSJD), Barcelona, Spain, between 2012 and 2016.

Results: Six cases were identified. All the 6 cases (100%) had a significant history for early pregnancy losses. Two patients had a previous history of recurrent pregnancy losses (>3) prior to spontaneous preterm labor of growth restricted fetuses with pathological utero-placenta doppler studies (33.3% of cases). The common factor among all patients was the smoking habits for more than 5 cigarettes per day and early pregnancy losses in the first trimester. In addition, maternal blood analysis showed increased neutrophils percentages and absolute values in 80% of the cases. Placental histological examination was significant for diffuse infiltration of the intervillos space prominently with cluster of differentiation 68 (CD68) positive macrophages and variable amounts of fibrinoid material deposition.

Conclusion: The mononuclear nature of the inflammatory cell infiltrate and the fibrin deposition in the placenta suggests an immunological insult. Hence, we hypothesize that the maternal immune system plays a key role in these cases. Also, our report data is consistent with the known association of chronic histiocytic intervillositis and recurrent pregnancy losses and FGR. In addition, these results support the notion of the negative impact of maternal smoking on pregnancy and fetal growth. Herein, we recommend conducting further studies to unravel the unknown pathophysiology of this disease in order to improve pregnancy outcomes.

KEYWORDS: Chronic histiocytic intervillositis; Fetal growth restriction; Recurrent pregnancy loss.

INTRODUCTION

In 1987, chronic histiocytic intervillositis (CHI) of the placenta has been described for the first time as a rare placental lesion (less than 1% of pregnancies).1 Yet, the exact etiology of histiocytic intervillositis is still unknown. CHI is characterized with extensive infiltration of inflammatory mononuclear cells (monocytes, lymphocytes, histiocytes), from maternal origin, predominantly in the intervillos space of the placenta with the accumulation of non-circulating histiocytic cells. Currently, extensive body of evidence is correlating CHI to placental insufficiency related adverse pregnancy outcomes including high recurrent rate of pregnancy loss in subsequent pregnancies and FGR.2

To understand this rare condition, a retrospective case-cohort study was conducted intended to (a) identify the relevant obstetric characteristics of pregnancies complicated with CHI
and (b) to establish a correlation between the pathologic characteristics of interovillitis and the adverse pregnancy outcomes.

MATERIALS AND METHODS

Study Design

Cases of CHI from 2012 through 2016 were selected from the patients’ records of the Department of Obstetrics and Gynecology with cross reference with the Department of Pathological Anatomy at HSJD, University of Barcelona, Barcelona, Spain. The Hospital’s Institutional Review Board (IRB) approved the protocol. All the women signed an informed written consent. The methods were implemented according to approved guidelines. For each patient obstetrical data, parity, outcome of pregnancy and the mode of delivery were collected. Also, placental histology and immunohistochemistry data were retrieved from the Department of Pathological Anatomy.

Inclusion criteria

- All pregnant women admitted to HSJD from 2012 to 2016 for miscarriage and/or delivery where the pathology report can be retrieved.

Exclusion criteria

- Cases diagnosed with congenital malformations.
- Cases where deliveries have taken place in other hospitals.
- Cases with no pathological report.

Routinely, all products of conception and/or placental samples of adverse pregnancy outcomes are evaluated in the Department of the Pathological Anatomy as part of the standard clinical care. All placentas were fixed in paraffin/formaldehyde after basic gross examination. Placental blocks of the selected cases were retrieved. Serial sections (5 µm) of tissues embedded in paraffin blocks were prepared and stained with hematoxylin-eosin (Figures 1 and 2). Placental tissues were evaluated with a panel of antibodies CD68 (mononuclear phagocytic lineage), CD3 (T cells) and CD8 (cytotoxic cells). Immunostaining was performed using the standard immunohistochemical protocol. All the slides were examined by the same pathologist.

RESULTS

In this cohort of patients placentas examined at the Department of Pathological Anatomy, six cases of CHI were detected. Clinical characteristics of the 6 patients diagnosed with CHI are

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Race</th>
<th>Parity</th>
<th>Gestational Age</th>
<th>Pregnancy outcome</th>
<th>Fetal weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>Spain</td>
<td>G6P1</td>
<td>8.6 Weeks</td>
<td>Abortion</td>
<td>------</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>Spain</td>
<td>G3P1</td>
<td>33 Weeks</td>
<td>Severe FGR</td>
<td>1290</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>Spain</td>
<td>G3P1</td>
<td>11 Weeks</td>
<td>Abortion</td>
<td>------</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>Latin</td>
<td>G5P1</td>
<td>8 Weeks</td>
<td>Previous history of Abortion</td>
<td>2100</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>Spain</td>
<td>G2P0</td>
<td>12 Weeks</td>
<td>Abortion</td>
<td>------</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>Spain</td>
<td>G2P0</td>
<td>8 Weeks</td>
<td>Blighted Ovum</td>
<td>------</td>
</tr>
</tbody>
</table>

G: Gravidity, P: Parity, FGR: Fetal growth restriction.

Table 1: Perinatal data.
shown in Table 1.

The mean age of the patients is 34 years. Racial composition is mostly of European decent, however, one patient is Latino (16.7%). Medical history was unremarkable except for recurrent pregnancy losses in the 1st trimester in 5 cases (83.3%). Four of the patients had a history of recurrent pregnancy loss and prenatal smoking >5 cigarettes per day (66.7% of patients). None of the cases had a history of travelling to malaria endemic areas. Two cases of the 6 (33.3%) had both recurrent pregnancy losses (>3 recurrent successive losses) and preterm delivery of growth restricted fetuses with pathological uterine doppler.

Maternal peripheral blood differential count analysis, of the 1st trimester, showed increased neutrophils percentages and absolute values in 5 cases (83.3%), decreased eosinophils and lymphocytes percentages in all cases (100%). Severe FGR complicated 2 pregnancies, and recurrence of CHI in subsequent pregnancies was documented in 5 cases (83.3%). All of the described 1st trimester cases with CHI had normal karyotype.

To summarize some of the most important findings: 66.3% of patients carried a diagnosis of recurrent spontaneous abortion (3 or more consecutive losses), 33.3% of all gestations reaching the 2nd or 3rd trimester had FGR.

All of the tested cases showed uniform immunohistochemical staining for CD68. The latter is an antigen uniformly expressed in cells of the mononuclear phagocyte lineage which confirmed the histiocytic origin of the infiltrate (Figure 2). Also, all placental pathology exams showed mononuclear cellular infiltrate, predominantly histiocytic, in the intervillous space (Figure 2) and intervillous fibrinoid deposition with intermediate trophoblast (Figure 4), a common finding in first trimester examined placentas. All cases have been examined to exclude any placental infections including viral or malarial.

**DISCUSSION**

CHI is a rare disease of unknown etiology. Placental lesions are characterized with mononuclear cells intervillous infiltrate and intervillous extensive fibrinoid deposit (Figures 2 and 3). A few T-cells and eosinophils may be present; and trophoblastic necrosis is a variable features.

In the literature, other minor forms have been described as the histiocytes accumulate in few areas of the placenta, called focal CHI. Various inflammatory patterns of chronic villitis have been documented including lymphohistiocytic, lymphocytic, lymphoplasmocytic lesions, and granulomatous inflammation with multinucleate giant cells. Meanwhile, CHI and villitis of unknown etiology (VUE) may coexist as they share some similarities such as histiocytic predominance. However, the intervillous infiltrate in VUE is polymorphic, consisting mainly of mononuclear cells of varying morphology, lymphocytes, giant cells, necrosis, fibrosis, granulation tissue and occasional neutrophils in the villous stroma. Mostly, these cells congregate near the villi rather than in the intervillous space. It is considered a common finding in normal and complicated pregnancies, hence it is believed that VUE may have an immunological origin.

CHI has been diagnosed in some cases with malarial infection. However, placental malariais differentiated by the presence of histiocytes containing pigmented depositions of hemato-
zoa or parasitized erythrocytes and there is usually also evidence of villous damage.\(^8\) Furthermore, neutrophils and areas of villous syncytial necrosis are generally observed, and fibrin deposits in malaria lack the fibrinoid character and intermediate trophoblast seen with CHI. In all our 6 cases, none of our patients had a travel history to malaria-endemic areas and the malaria infection was excluded after placentation examination. Viral placental infections should be included in the differential diagnoses as well. However, they display significant intervillitis and exhibit diffuse villitis and villous scarring. Intervillositis in these infections is mainly neutrophilic predominance and associated with acute villitis or intervillous abscess formation. These findings were not noted in our placental exams. One last idiopathic placental lesion is the maternal floor infarction, which is easily diagnosed by the deposition of fibrin in the decidua beneath the placenta rather than arterial occlusion and ischemic necrosis of the villi and not including any inflammatory component.\(^9,10\)

CHI has no specific clinical symptoms and signs suggesting its diagnosis. However, CHI has a high tendency for recurrence and increased rates of unfavorable perinatal outcomes including recurrent spontaneous abortions, perinatal mortality and FGR. The only biomarker which can be used to detect CHI is alkaline phosphatase (ALP); yet the latter is not specific to CHI placental malfunction. In a study of 211 placentas, the incidence of CHI was increased among the low birth weight in CHI placental malfunction. In a study of 211 placentas, the incidence of CHI was increased among the low birth weight infants of all the studied cases.\(^13\) In another study, it was noted that villitis was the most frequent pathologic placental finding in normotensive-term pregnancies with FGR.\(^14\) Therefore, it has been recommended that chorionic villus sampling may be performed to evaluate both CHI and karyotyping in all pregnancies with severe FGR.

It has been postulated that an immuno-inflammatory trigger is a possible pathomechanism of CHI due to (a) the presence of maternally derived mononuclear cells, (b) increased presence of inflammatory cells, and (c) the presence of acute atherosis-like lesions in the decidual vessels with Immunoglobulin M (IgM) and complement deposits.\(^15\) Another piece of evidence that supports the above mentioned notion is that CHI has been reported to be associated with antiphospholipid antibodies and systemic lupus erythematosus. These morbidities have been known to trigger the maternal immune system.\(^16\) Others have considered pregnancy as an allograft bearing foreign, paternally derived antigens transplanted into the maternal uterus.\(^7\) Hence, suppression or modulation of the maternal immune reaction to these foreign antigens is mandated to protect the fetus. One of the fetal protection postulated mechanisms is deviation of the maternal local inflammatory cells away from a delayed hypersensitivity-type response (known as TH1) towards a TH2-type response.\(^17\) Simultaneously, the placenta is infiltrated by maternal immune cells: macrophages, T-lymphocytes, and natural killer (NK) cells early in pregnancy to support maternal tolerance to paternal antigens.\(^18\) As a result, maternal activated macrophages, lymphocytes (CD3+) cells, and specific cytokines, such as gamma-interferon and tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), are strictly regulated within the placentas. That may explain the presence of mononuclear cells in the placentas of CHI.

It is well known that during gestation neutrophil counts gradually increase starting from the 1\(^{st}\) trimester and the lymphocyte count tends to decrease by the end of gestation.\(^19\) Our data showed increased neutrophils count (percentages and absolute values) in 5 cases (83.3%), decreased eosinophils and lymphocytes percentages in all cases (100%) in the first trimester maternal peripheral blood testing in comparison to normal gestational aged matched pregnancy. Given our limited number of cases, however it may suggest an exaggerated maternal immune-inflammatory response associated with CHI cases.

Furthermore, it is believed that the inflammatory process in CHI leads to luminal obliteration and/or thrombosis, resulting in avascular villi. However, the stronger impact of immunological changes is suggested to play the major role. Of note, CHI has been shown to be associated with assisted reproductive techniques in very small percentages of cases.\(^20\) What triggers these immunologic events is obscure, but the presence of villitis in normal placentas supports the above mentioned notion.

Owing to the high recurrence rate of the lesion, and CHI does not present with any specific symptoms during gestation, it is recommended that these patients should be treated as being at high risk in their subsequent pregnancies. Though, there is no established therapeutic protocol and the assumption of immune mechanism is involved in the pathogenesis of placental lesions has led to the proposal of immunosuppressive and thrombolytic therapy. Also, treatment with corticosteroids and aspirin has been attempted in few cases.\(^21\) However, due to the rarity of the disease, there is not sufficient data to support such treatment. Hence, more studies are required in order to understand the mechanism of CHI and its management.

We acknowledge the limitations in this review as the number of diagnosed cases is limited, due to the rarity of the condition. However, in this report, we present new evidence for the association between CHI and adverse pregnancy outcomes particularly, FGR. Furthermore, to our knowledge, this is the
first article showing clinical signs during gestation in cases of CHI: the abnormal Doppler studies. Also, we have shown differences in the maternal peripheral blood immune cells in cases of CHI in comparison to the controls in the first trimester. This may suggest either that the maternal immune system has been prematurely triggered resulting in placental pathology or cases of CHI has an early influence on the maternal immune cells.

CONCLUSION

CHI is a rare disease of unknown etiology. It is only diagnosed postnatal. Yet, CHI has a big impact on the female reproductive capacity. The condition has a high recurrence risk in subsequent pregnancies, associated with pregnancy losses, and FGR. Hence, it is essential to recognize CHI and report it once diagnosed. Moreover, it is essential to differentiate CHI from chronic villitis and other forms of placental lesions.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

CONSENT

The authors obtained written informed consent from the patient for submission of this manuscript for publication.

REFERENCES


Female Genital Schistosomiasis: A Neglected Tropical Disease

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ABSTRACT

Female genital schistosomiasis is a neglected tropical disease. Few clinicians consider it in their differential diagnosis. Yet this disease affects hundreds of millions of people. Hundreds of thousands of them actually die annually. It significantly affects the reproductive health of women. Patients infected in childhood may carry the burden of disease throughout their lives without being detected. Global attention is occupied by new emerging diseases like Zika virus and female genital schistosomiasis is relegated to back of pages in the list of global worries. The importance of this disease on the health of women cannot be over-emphasised. The global attention must be focused so that it can be tackled adequately. Awareness among clinicians must be increased so that they consider it when women present to them with unusual symptomatology.

Female genital schistosomiasis is a neglected tropical disease affecting millions of people. It causes significant morbidity and mortality in women. Awareness among clinicians is low as most cases are discovered fortuitously while undergoing investigations for other conditions.

KEYWORDS: Female genital schistosomiasis; Neglected disease; Morbidity; Mortality; Life-threatening.

INTRODUCTION

Schistosomiasis is a neglected tropical disease despite the fact that it affects 200 million people causing profound morbidity and mortality. It is a poverty related problem.1 Annually more than 200,000 people die from the disease. It is endemic in riverine areas of the world such as Africa, Eastern Mediterranean, Central America, East Asia and the Middle East.2 Travellers to these areas can be affected. The majority of genito-urinary infections are caused by Schistosoma haematobium, Schistosoma japonica and Schistosoma mansoni that is found in Brazil.4 It is important to bring this topic to global attention as the patients may suffer asymptomatic disease burden.

PATHOGENESIS

Schistosoma are parasitic trematode blood flukes of the family Schistosomidae affecting the urinary and gastro-intestinal tracts.2 Humans get infected by getting into contact with infected waters. The eggs of the flukes spread haematogenously, embolising to the liver, spleen lungs and brain. In the genitourinary system in the early stages it primarily involves the bladder and ureters but later the kidneys and genital organs are involved.2 It rarely infects the colon or the lungs. The ova lodged in the tissues causes a tissue reaction in the genital mucosa.5

This article describes the effects of the schistosoma on the female genitourinary system. Ova have been described in the cervix,7 uterus, fallopian tubes, ovaries and bladder. Ova in the genital mucosa may cause lesions.7 The lesions seen in infected tissue have been described as circular, reticular, branched, convoluted, granny or sandy areas.8-10 Lesions that develop in childhood are chronic.
CLINICAL PRESENTATION

Female genital schistosomiasis may be asymptomatic. Female genital schistosomiasis may cause abnormal malodorous vaginal discharge, contact bleeding, dysmenorrhea, menorrhagia, dysuria and haematuria. In the vulva patients may complain of lumps or chronic itching. Patients may present with chronic pelvic pain. These symptoms can occur in sexually transmitted infections, benign and malignancy conditions causing confusion and delayed or misdiagnosis.

ASSOCIATIONS

Schistosomiasis infection is associated with human papillomavirus and human immunodeficiency virus in causing abnormal Pap smears and cervical cancer. Tissue reaction to ova in mucosal lining assists in HIV infection. In a study in Zimbabwe women with genital schistosomiasis had an almost three-fold risk of having HIV infection. Schistosomiasis infection has long been linked to development of squamous cell bladder cancer.

COMPLICATIONS

Infected person suffer from chronic anaemia and malnutrition. The complications of this infection include ureteritis, pyelitis and cystitis. There could be calcification, fibrosis and strictures in the urinary system. Genital tract infection may cause chronic pelvic inflammatory disease and subfertility as the ova are lodged in the Fallopian tubes (Figure 1). This can lead to ectopic pregnancies. Ectopic gestations can rupture causing catastrophic bleeding and demise. Neglected tropical diseases like schistosomiasis can have a profound impact on women’s reproductive health. Many cases of unexplained pregnancy losses may be due to undiagnosed neglected tropical diseases. Genital tumours such as ovarian pseudo tumours can occur. Chronic schistosomiasis infection causes vulval/labial lesions (Figure 2), fibrosis, cervical lesions/dysplasia and organomegaly.

DIAGNOSIS

The diagnosis of female genital schistosomiasis can be missed altogether as few clinicians consider it in their day to day work. This is due the fact that is now a neglected disease way down the list of the world attention. The diagnosis is sometimes made fortuitously when investigating the clinician’s usual conditions. Urine dipstick can reveal haematuria. Urine microscopy is the next step in the diagnostic route to do. At times routine Pap smear tests can reveal genital schistosomiasis (Figure 3). Polymerase chain reaction on vaginal lavage samples or urine was found to be a better was to diagnose female urogenital schistosomiasis compared to cytology.

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Figure 1: Fallopian tube heavily infected with schistosoma ova.

Figure 2: Schistosoma ova in a labial skin biopsy.

Figure 3: (A) Schistosoma ova and (B) severe cervical dysplasia.
An abdominopelvic x-ray can reveal calcifications. Computed tomography, intravenous urography, computed urography may all reveal bubble-like filling defects representing ova deposited in ureters, kidneys and bladder.1

Directed punch biopsies obtained cystoscopically, hysteroscopically and colposcopically sent for histopathological examination can be diagnostic.

PREVENTION

Many countries are working towards eliminating the disease by destroying the snail habitat. The provision of clean water reduces schistosome infection. Public health education may reduce disease burden.

TREATMENT

The cornerstone of schistosomiasis control is mass single dose praziquantel treatment in high prevalence areas.24 The adult population is the most important target group. For school-age children, the WHO approves the dose pole for praziquantel dosing based on height. The other drug is oxamniquine but it costs more than praziquantel. The public health importance of female genital disease importance is not adequately addressed.25

RESEARCH ADVANCES

Recent research into the mechanisms of immune regulation has provided new insight into immune responses to chronic diseases. Studies on host genetics, T-helper cell type 1 or 2 cytokines influencing immunity and granuloma formation have provided relevant information. There is on-going research to develop a schistosoma vaccine that will prevent the parasite from completing its life cycle in humans.

CONCLUSION

Female genital schistosomiasis is an important, tropical and neglected disease affecting millions of people. Global attention should be brought back so that it is tackled adequately thereby reducing the morbidity and mortality in women. Awareness amongst clinicians must be encouraged so that it is considered in the clinical setting to avoid delayed or misdiagnosis and appropriate chemotherapy given.

AUTHOR’S CONTRIBUTION

This is the sole work of Mr. S. Ngwenya.

REFERENCES


Pelvic Actinomycosis Masquerading as Malignancy

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INTRODUCTION

Pelvic actinomycosis is a chronic granulomatous suppurative disease caused by Actinomyces israeli. The opportunistic anaerobic bacterium Actinomyces israeli is a normal part of the human flora in the oropharynx, gastrointestinal and genital tract. More than 50% of actinomycosis infections occur in the craniofacial region. Pelvic infection accounts for 20% of human cases. Abdominal-pelvic actinomycosis is often mistaken for other conditions, presenting a pre-operative diagnostic challenge. The infection mimics ovarian tumors and tuberculosis and is diagnosed only after surgery in most of the cases. Actinomycosis secrete proteolytic enzymes, disrupt tissue planes and compress surrounding tissues which makes their presentation closer to a malignant process. Slow growing nature of actinomyces, non-specific clinical presentation and extensive spread before the diagnosis is made often pose a clinical challenge. Owing to slow growing nature and chronic inflammatory process, pre-operative diagnosis is difficult and is often made retrospectively after surgical debulking. Infection is rare in infants and children. Many cases are found in women using intra-uterine contraceptive device (IUCD). Actinomycosis is 3 times more common in men than women. Alcoholism, intravenous drug abuse, peptic ulcer, and biliary tract disease are risk factors for actinomycosis. It is most commonly found in regions of low socio-economic status and poor hygiene.

We review a case of pelvic actinomycosis that was managed at the Obstetric and Gynecology Department of K. J. Somaiya Hospital, Mumbai, India.

CASE REPORT

A 50-year-old lady sought gynecological opinion for lower abdominal pain. She gave a history of vague abdominal pain of 6 months which had aggravated over 2 months period. She was post-menopausal since 3 years. Her previous cycles were regular. Our patient was a housewife with 2 children. There was no history of IUCD usage or medical termination of pregnancy (MTP). Patient did not give history of tuberculosis, pelvic inflammatory disease (PID) or any other significant illness in the past. She had history of decreased appetite and loss of 15 kgs of weight over a period of 1 year. On examination patient was pale. Per vaginal examination showed a normal size anteverted uterus with restricted mobility and a vague mass in the left adnexa non-seperable from the uterus. Right fornix was free. No lymphnodes were palpable. Blood investigations showed Hb value of 8.3 gm/dl and ESR-130 mm/1ST hr. Cancer antigen 125 (CA-125) was within normal range. Serial sonographic studies and computerized tomography (CT) scan revealed an irregular high density thick walled heterogeneous complex cystic mass lesion in the left adnexa with left ovary not seen seperately from the lesion, measuring 6×6×3 cms with multiple thin internal echos and small calcifications. Few internal septae dividing the cyst into loculations were also noted. Pre-operatively there was a mass in the left adnexa which was twisted and dense adhesions were seen between adnexa, posterior surface of the uterus and rectum. Mass was separated and intraoperative rupture of mass revealed pus like material. The pre-operative diagnosis was kept of borderline or early malignant ovarian lesion. Total Abdominal Hysterectomy and bilateral salpingo-oophorectomy was done.

The gross specimen showed a left tubo-ovarian mass measuring 7×3×3 cms and cut section showed whitish exudate and granular surface. Endometrium showed a polypoidal thick-
ening throughout. But the uterus, right ovary and tube did not show any significant pathology. Initial histological evaluation revealed dense xanthogranulomatous inflammation with suppurations, eosinophilic abscesses and fungal hyphae with septae and branching, left tube showed lymphoid aggregates and xanthomatous inflammation resembling morphology of fungus aspergillosis. Cytology of ascitic fluid did not detect malignant cells. Patient was initially treated with intravenous ceftriaxone and metronidazole followed by oral therapy for 5 days.

DISCUSSION

Actinomycosis is certainly under-reported as a consequence of diagnostic errors, difficulties in confirming the disease, and the empirical utilization of antibiotics. Actinomycosis often presents with vivid presentations that can mimic various etiologies like tuberculosis, nocardiosis, malignancies.

Our patient was a post-menopausal patient with complex pelvic mass, normal CA-125 levels with raised erythrocyte sedimentation rate (ESR) and history of weight loss, so clinical dilemma between malignant and chronic inflammatory conditions existed. Significant weight loss pointed towards malignant etiology whereas raised ESR suggested of chronic inflammatory condition. Absence of IUCD kept us from diagnosing actinomycosis. Pelvic actinomyces often has complicated presentations as in our case, the mass was pointing towards the malignant etiology. Radiological investigation further added to clinical dilemma with complex tubo-ovarian mass with thick internal echoes pointing towards inflammatory condition and loss of tissue planes indicating malignant etiology. Actinomycosis often leads to complex pelvic masses with loss of tissue planes which are difficult to diagnose preoperatively. Intraoperative finding of caseous yellow exudate and pus from the adnexal mass was the 1st objective evidence of inflammatory condition in our case. Failure to diagnose this intraoperatively may lead to extensive debulking surgery as is commonly performed for ovarian cancer with morbidity and loss of organ function. Pelvic actinomycosis has previously been noted to mimic ovarian malignancies. The diagnosis of pelvic actinomycosis is challenging with only 10% of cases diagnosed pre-operatively. This is because of a similar presentation to other common conditions such as malignancies, tuberculosis, or Crohn disease. Pelvic actinomycosis can occur at any age and in a reported large cohort of 92 patients, the mean age at diagnosis was 37 years.

The presenting features usually include fever, pelvic pain or the incidental findings of suspicious pelvic masses on imaging. Ultrasound and CT are the most commonly used imaging modalities for diagnosing pelvic actinomycosis; however, findings are usually nonspecific and thus unreliable in assisting in the differential diagnosis. CT findings in women with abdominal actinomycosis show predominantly solid masses with focal areas of reduced attenuation or thick-walled cystic masses. Our patient presented with a unique symptom of vague abdominal pain in combination of significant weight loss. Owing to paucity of clinical clues preoperative diagnosis was in doubt hence with patients of complex tubo-ovarian masses with features unclear of malignant or inflammatory etiology a strong suspicion of actinomycosis should be made. Preoperative diagnosis of actinomycosis in a complex tubo-ovarian mass is difficult owing to difficulty in visualizing actinomyces in routine H&E histopathological sections (Figure 1). Actinomyces filaments demand special stains like Grocott-Gomori-Methanamine-silver nitrate stain, Brown-Brenn stain. Immunofluorescence techniques also can facilitate actinomyces from tissue sections. Key point in diagnosing actinomycosis is increases awareness among treating physicians and awareness regarding correct sampling and submission of tissue samples. Actinomyces is susceptible to various anti microbial agents like penicillin G, erythromycin, clindamycin, chloramphenicol, cephalosporins. Complicated actinomyces infection needs treatment with intravenous penicillin G intensive phase followed by oral penicillin V cover. Patients allergic to penicillin V can be treated with other second line drugs. Owing

Figure 1: H&E staining of Tuboovarian mass showing actinomyces filaments.
to chronicity and possible relapse of the condition, long-term antibiotic cover, duration of the same is still not clear.8,9

Combined medico surgical approach helps treating complex actinomyces infection. There are no specific measures to prevent actinomycoses, although maintaining personal hygiene, good orodental care, removing dental plaques can help to reduce density if not incidence of colonization.

CONFLICTS OF INTEREST

The authors have declared that they have no conflicts of interest.

CONSENT

The authors have received the written permission for the publication of this case detail.

REFERENCES


