Prolonged Aminoglycoside Treatment for Pelvic Inflammatory Disease Associated Ovarian Carcinoma

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ABSTRACT
Pelvic actinomycosis constitutes one of the curiosities of gynecology. In this present investigation the presence of actinomycetes infection among Intrauterine device (IUD) users and its correlation correlated with the development of Pelvic Inflammatory Disease (PID) and ovarian carcinoma was studied. Endocervical swabs were obtained from ovarian carcinoma, IUD users, non-users and processed to isolate actinomycetes on actinomycetes isolation agar. The isolation rate was found to be increased among IUD users who were clinically diagnosed to have PID (52.9%) followed by ovarian carcinoma cases who were prior users of IUD (44.4%). Compared to healthy non-IUD users, IUD users with PID experienced a 158 fold statistically significant increased risk of actinomycetes infection (OR = 158.63, 95% CI = 17.84, 161.11) followed by ovarian carcinoma patients with IUDs (OR = 112.80, 95% CI = 10.59, 120.02). The isolates showed high resistance against penicillin, clindamycin and erythromycin and low resistance against tetracycline, linezolid and gentamycin. The use of IUDs facilitates the colonization by actinomycetes which in turn lead to PID and pelvic actinomycosis. Further the pelvic actinomycosis simulates pelvic malignancies. If chronic actinomycetes infection are encountered, the patients should be given long term therapy with aminoglycoside antibiotics and if a pelvic mass is evident aggressive and prolonged antibiotic therapy with surgical intervention is required.

Key words: Ovarian carcinoma, IUD, PID, aminoglycoside

INTRODUCTION
Actinomycosis is one of the rarer forms of infection of the human tissues usually caused by Actinomyces israelii, but also caused by A. bovis and A. ericksonii. These bacteria are part of endogenous microflora in the oro-pharyngeal cavity and become pathogenic when they enter the peritoneal cavity (Hamid et al., 2000). Pelvic actinomycosis constitutes one of the curiosities of gynecology. The route of pelvic infection by actinomycetes was formerly thought to be by extension from established ileocaecal disease but several studies have suggested the presence of an Intrauterine device (IUD) as a possible source of infection. Pelvic actinomycosis accompanied by IUDs accounts for about 3% of all actinomycosis (Polat et al., 2008).
Actinomycosis infection leads to tissue granulation, dense fibrosis and abscess in the pelvis. It can produce a hard mass in the pelvis and may compress the ureter or intestines. Thus the clinical findings of pelvic actinomycosis are similar to those of tubo-ovarian abscesses or pelvic malignancies. In addition to this there are reports that depict actinomycosis to simulate pelvic malignancies particularly advanced ovarian carcinoma (Gungor et al., 2013).

Although a history of Pelvic Inflammatory Disease (PID) was correlated to a higher risk of ovarian cancer in a case-control study (Ertas et al., 2014) such persistent infections leading to chronic inflammation in the pathogenesis of ovarian cancer have always been overlooked. Given the incomplete biological explanations for the aetiology of ovarian cancer and the hypothesis of chronic infection and inflammation as a part of ovarian tumour pathogenesis, we report here the infection of actinomycetes among women with IUD associated PID and ovarian cancer on comparison with non-IUD users.

**MATERIALS AND METHODS**

A total of 51 women with clinical diagnosis of ovarian carcinoma were found through the oncology department of Dr. G. Vishwanathan Institute of Cancer from May, 2010 to November, 2011. During the same study period, 67 married women were selected from patients referring to Gynaecological and Obstetrics unit of Pankajam Seetharaman Hospital, Tiruchirapalli, Tamilnadu, India for removal of IUD. Reasons for removal were PID, haemorrhage, pelvic pain, vaginal discharge, desire to conceive or an IUD in utero for 2 years or more. A total of 118 women were thus recruited and divided into 4 groups according to clinical findings. Group A (9) had Ovarian Cancer (OC) and history of IUD usage, group B (42) had OC and non-IUD users, group C (17) had PID and IUD users, group D (50) asymptomatic IUD wearers.

One hundred and forty two women attending Gynaecological and Obstetrics unit of Pankajam Seetharaman Hospital for advice on contraception were recruited as controls. The criteria for controls were non-IUD users, not currently pregnant had an intact uterus, no current referral of hysterectomy or cervical conisation, reported no use of vaginal medication, reported no treatment of gynaecological disease in the previous 6 months, reported no diagnosis for anogenital cancer and tobacco related disease. All recruited women received detailed information regarding the objective of the study and gave written consent to participate. The study has been approved by the Institutional Ethics Committee of Bharathidasan University (DM/2011/101/20).

The cervix of each patient was exposed by sterile bivalve speculum and endocervical swabs were obtained with sterile cotton swabs. These sites were sampled as they represent areas where the IUD lies. The swabs were then placed on sterile thiglycolate broth and transported to the laboratory on ice for further processing on the same day. The transported swabs were streaked directly on actinomycetes isolation agar containing nalidixic acid and nystatin (80 mg L⁻¹) and incubated at 37°C for 3 weeks. The microbial growth from the case patients and control subjects was evaluated qualitatively every week. The actinomycetes colonies were identified by their colony morphology and pure cultures were obtained by sub-culturing on actinomycetes isolation agar. The actinomycetes were identified based on their morphological and biochemical characteristics (Cappuccino and Sherman, 2002).

The data were coded and analyzed using the SPSS package. Univariate analysis was undertaken to screen potentially significant risk groups. The case control analysis of the data, odds ratio and the corresponding 95% confidence intervals was calculated by unconditional logistic regression and maximum likelihood estimation. Tests of statistical significance were based on difference in the log likelihoods and all p-values are 2 sided.
Table 1: Odds ratios, confidence intervals and p-values for different subject groups associated with actinomycetes infection among women from the study population

<table>
<thead>
<tr>
<th>Groups</th>
<th>No of cases</th>
<th>Actinomycetes isolation</th>
<th>OR (95%) CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td>112.80 (10.59, 120.02)</td>
</tr>
<tr>
<td>B</td>
<td>42</td>
<td>1</td>
<td>41</td>
<td>3.44 (0.210, 5.62)</td>
</tr>
<tr>
<td>C</td>
<td>17</td>
<td>9</td>
<td>8</td>
<td>158.63 (17.84, 161.11)</td>
</tr>
<tr>
<td>D</td>
<td>50</td>
<td>6</td>
<td>44</td>
<td>19.23 (2.253, 64.06)</td>
</tr>
<tr>
<td>E</td>
<td>142</td>
<td>1</td>
<td>141</td>
<td>1.00 (Ref)</td>
</tr>
</tbody>
</table>

RESULTS

Seventeen (22.4%) and 9 (11.8%) patients with IUDs or past history of IUDs were diagnosed clinically as having PID and ovarian cancer, respectively. Four (44.4%), one (2.4%), nine (52.9%), six (12%) and one (0.7%) actinomycetes were isolated from group A, B, C, D and E, respectively. Table 1 summarizes the risk of actinomycetes infection among various group of patients. A significant association was observed between the actinomycetes infection and the use of IUD. Compared to healthy non-IUD users, IUD users with PID experienced a 158 fold statistically significant increased risk of actinomycetes infection (OR = 158.63, 95% CI = 17.84, 161.11). One hundred and twelve and 19 fold increased risk of actinomycetes infection was observed among IUD users with ovarian cancer (OR = 112.80, 95% CI = 10.59, 120.02) and asymptomatic IUD users (OR = 19.23, 95% CI = 2.253, 64.06), respectively.

DISCUSSION

Actinomycosis is a chronic, suppurative and granulomatous bacterial infection caused by Actinomyces israelii. These species are endogenous microflora of the human oropharynx, gastrointestinal tract, dental caries and tonsillar crypts. They are not generally considered part of normal vaginal flora but rather are associated with the presence of a foreign body most often an IUD. The IUD promotes colonization of actinomycetes species. Furthermore the insertion of IUD breaches the protective barrier of cervical mucus and its tail creates a transmission link between the sterile uterine cavity and bacteria rich vagina. Thus the ecological changes triggered by the foreign body play a crucial role in the development of IUD-associated PID.

Several studies (Sran et al., 2012; Zardawi, 2014; Steenland et al., 2013) have linked PID with ovarian cancer risk. In the present study actinomycetes isolation has been facilitated in nearly 4 (44.4%) of the ovarian carcinoma patients who were IUD users. Of these 4 cases, 3 reported to have a previous clinical history of PID. Through the present study we propose a hypothesis of simulation of ovarian carcinoma by actinomycetes species that have colonized the IUD. The use of IUDs facilitates the colonization by actinomycetes which in turn lead to PID and pelvic actinomycosis. Further the pelvic actinomycosis simulates pelvic malignancies. Pelvic actinomycosis usually occur following bowel perforation, especially perforation of the appendix due to appendicitis, but the ascending route from the lower genital tract is thought to be important for the infection (Nasu et al., 2002). Previous study has reported ovarian actinomycosis as a very rare event as the structure of the ovary is resistant to surrounding inflammatory disease. But it can be assumed that these bacteria get trapped in the inclusion cysts in which ovarian surface epithelium becomes entrapped in the ovarian stroma and differentiates, proliferates and undergoes malignant transformation. Furthermore, PID appears to increase the likelihood of occurrence of these types of cysts although not necessarily inclusion cysts.
Antibiogram of the isolates from IUD users showed high resistance to penicillin antibiotics belonging to natural penicillin’s group and are highly sensitive towards amino glycosides group. Penicillin antibiotic which has long been used for treatment of actinomycosis has shown considerably less activity in vitro and should probably be avoided for management of patients with actinomycosis. Aminoglycosides antibiotics in particular tetracycline, linezolid and gentamycin appear to be excellent alternative therapies when penicillin fails or the patient is unable to tolerate this drug (Fig. 1).

In conclusion the latency period of the IUD insertion and actinomycetes infection can vary and a careful history may help to make clinical suspicion of this entity. Once the diagnosis has been confirmed, the patients should be given long term therapy with aminoglycoside antibiotics. If a pelvic mass is evident aggressive and prolonged antibiotic therapy with surgical intervention is required.

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