Educational Case

Educational Case: Pelvic actinomycosis masquerading as an ovarian tumor

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These competencies are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.journals.elsevier.com/academic-pathology/pathology-competencies-for-medical-education-pcme.1

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Primary objective

Objective FO2.1: Infections Involving the Ovary. Describe the pathogens, bacterial, fungal, and parasitic that can cause ovarian disease and explain the underlying mechanisms, clinicopathologic features, and complications.

Competency 2 Organ System Pathology; Topic: Female Reproductive—Ovary (FO); Learning Goal 2: Non-neoplastic Disorders of the Ovary.

Secondary objective

Objective FU4.1: Clinical Features of Pelvic Infections. Discuss the common pelvic infections, including those affecting the vulva, vagina, cervix, and fallopian tubes, and describe the pathogenesis of pelvic inflammatory disease, common organisms involved, and its complications.

Competency 2 Organ System Pathology; Topic: Female Reproductive—Uterus (FU); Learning Goal 4: Female Genital Tract.

Patient presentation

A 44-year-old multiparous woman presents with a chief concern of lower abdominal pain and lack of appetite for three months. The pain is not accompanied by fever or vaginal discharge. She describes the pain as a dull ache that comes on and off and is aggravated by physical activity and relieved by rest. Upon questioning, she states that the pain is non-cyclic and not triggered by the onset of menstruation. Her menstrual periods are regular, and her last Pap smear, carried out a year ago, did not reveal any abnormalities. Her last childbirth was 12-year ago. She had a copper intrauterine device (IUD) for contraception inserted six-year ago. She has noticed a 4-lb weight loss in the past six months. She denies nausea, vomiting, heartburn, diarrhea, constipation, or bloody stools.

Diagnostic finding, Part 1

On physical examination, the patient is afebrile, and her vital signs are within normal limits. Her abdomen is soft and non-distended. She displays focal bilateral lower quadrant tenderness on palpation but no rebound tenderness. A bimanual pelvic examination reveals palpable bilateral adnexal masses, each measuring 6 x 5 cm, which is firm and tender.

Questions/discussion points, Part 1

Based on the clinical history and physical exam, what is the differential diagnosis?

This patient presents with lower abdominal pain along with bilateral palpable firm adnexal masses. Adnexal masses can be neoplastic or non-neoplastic. Common benign tumors include serous and mucinous cystadenoma.2 Other rare benign tumors include leiomyoma and ovarian sex-cord stromal tumors, such as fibroma and thecoma.2 Malignant primary ovarian tumors that are epithelial-derived have a high incidence of bilaterality. This includes serous and mucinous cystadenocarcinomas, which are often accompanied by ascites. Germ cell tumors and sex-cord

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tumors rarely involve both ovaries. Bilateral metastasis (Krukenberg tumor) from an occult primary signet ring adenocarcinoma originating from gastric or colorectal cancers should also be considered in the differential diagnosis.

Moreover, non-neoplastic conditions are also a possibility and should be ruled out. With a history of IUD use in this patient, pelvic inflammatory disease (PID) is a likely possibility. In the absence of fever, chronic infections, such as tuberculosis, may be suspected if the patient is from a location of high incidence. Endometriosis of the ovary presents with abdominal pain but typically coincides with menstruation and may also present as infertility. If unilateral pelvic pain manifests in the patient, left- or right-sided diverticulitis and acute appendicitis, respectively, should be considered. Acute appendicitis is unlikely, given a history of a three-month duration of pain. Ectopic pregnancy should be suspected if the patient’s CA-125 levels are not above 200 U/mL, her weight loss and bilateral adnexal masses could be concerning for an ovarian malignancy. Moreover, non-neoplastic conditions are also a possibility and should be ruled out. With a history of IUD use in this patient, pelvic inflammatory disease (PID) is a likely possibility. In the absence of fever, chronic infections, such as tuberculosis, may be suspected if the patient is from a location of high incidence. Endometriosis of the ovary presents with abdominal pain but typically coincides with menstruation and may also present as infertility. If unilateral pelvic pain manifests in the patient, left- or right-sided diverticulitis and acute appendicitis, respectively, should be considered. Acute appendicitis is unlikely, given a history of a three-month duration of pain. Ectopic pregnancy should be suspected if the patient’s CA-125 levels are not above 200 U/mL, her weight loss and bilateral adnexal masses could be concerning for an ovarian malignancy.

Diagnostic findings, Part 3

Due to a suspicion of bilateral ovarian malignancy, the patient undergoes a total hysterectomy with bilateral salpingo-oophorectomy. During laparotomy, both ovaries are enlarged. No adhesions, fluid, or pus are found in the pelvic peritoneum. The specimens are subjected to histopathological examination.

Questions/discussion points, Part 3

Figures 1 and 2 show one of the ovaries. Describe the gross and histologic features.

A gross examination of this ovary shows a mass (6 × 5 cm) that is predominantly solid and partially cystic. The center of the solid area is friable with purulent material. Microscopic sections (hematoxylin and eosin stain) show clumps of filamentous bacteria consistent with Actinomyces colonies. The bacterial colonies display a dark staining eosinophilic rim at the periphery, referred to as the “Splendore-Hoeppli” phenomenon, caused by immune complex deposits and cell debris. The bacterial colony is surrounded by suppurative inflammation, with the presence of numerous polymorphonuclear neutrophils.

What is PID?

PID refers to an infectious and inflammatory disorder of the female upper reproductive system. It involves the endometrium, fallopian tubes, ovaries, or the pelvic peritoneum. Infections are acquired either by ascending route from the vagina and cervix (most commonly) or hematogenous through the bloodstream. The infection is deep-seated and often presents subtle clinical signs and symptoms. Clinically, PID is classified as either acute, subacute (subclinical), or chronic.

Questions/discussion points, Part 2

Interpret the diagnostic studies of this patient

Laboratory data show mild leukocytosis and neutrophilia, suggesting the possibility of inflammation or infection. This is also supported by an increase in the levels of inflammatory markers, such as ESR and CRP. CRP levels in the intermediate range may suggest low-grade chronic inflammation. Pregnancy can be ruled out based on the normal beta-hCG levels. AFP and beta-hCG are tumor markers that may be elevated in some germ cell tumors. CA-125 and CEA levels may be elevated in epithelial ovarian malignancies. CA-125 may also be elevated in PID and endometriosis. Since the elevation of CA-125 levels occurs in both benign and malignant disorders, interpretation based on CA-125 levels should be made with caution. Malignancy should be suspected when CA-125 levels are above 35 U/mL in postmenopausal women or 200 U/mL in premenopausal women.

Ultrasoundographic findings that may indicate malignancy include a solid component, thick septations, and bilaterality. Although the patient’s CA-125 levels are not above 200 U/mL, her weight loss and bilateral adnexal masses could be concerning for an ovarian malignancy.

What is the diagnosis based on the pathologic findings?

Gross and microscopic images show features of PID with tubo-ovarian actinomycosis and abscess, consistent with the diagnosis of pelvic actinomycosis.

What is PID?
Clinicaly, many patients with acute PID present with an acute onset of fever, lower abdominal pain, abnormal vaginal discharge, uterine bleeding, dyspareunia, and dysuria. A bimanual examination can elicit cervical motion and uterine or adnexal tenderness.

Gross examination of the reproductive organs in severe acute PID reveals inflammation of the uterus and hyperemia of the serosa coated with fibrinous exudate. Inflammation and purulent exudate distort the tube and ovaries. A tubo-ovarian abscess or mass develops with both structures entangled in adhesions (Fig. 3).

Subacute or subclinical PID refers to an asymptomatic infection related to the same pathogens that cause acute PID. It occurs in women with previously diagnosed or undiagnosed acute PID. Infection results in structural and functional damage to the fallopian tubes. Clinically, most patients present with infertility.

Chronic PID can last for more than 30 days and is caused by a chronic infection due to Mycobacterium tuberculosis or Actinomyces species. Clinically, it is insidious and may present with chronic or intermittent pelvic pain, pelvic masses, abnormal uterine bleeding, low-grade fever, weight loss, and gastrointestinal and renal symptoms. Adnexal masses detected by clinical examination and imaging studies are often mistaken for neoplastic disease. The salient features of acute and chronic PID are presented in Table 1.

Describe the microbiological features of Actinomyces

Actinomyces are obligate anaerobic gram-positive bacilli. They are non-acid-fast and slow growing. There are several species of which Actinomyces israelii is the most common cause of disease in humans. Actinomyces reside as commensals in the human mouth, urogenital tract, and gastrointestinal tract. When mucosal barriers are breached, they invade and become pathogenic. The disease state of this infection is referred to as actinomycosis. Gram staining of the infected tissue reveals the branched filamentous nature of Actinomyces with radially arranged peripheral hyphae. Owing to the presence of filaments or hyphae, Actinomyces was originally thought to be a fungus. Actinomyces is classified as a true bacteria because it lacks mitochondria and a nuclear membrane. Actinomyces co-exists with as many as 5–10 companion bacteria, and the colonies contain a mixture of cocci and rods. Actinomyces is an opportunistic pathogen that is characterized by suppurative and granulomatous inflammation. Actinomyces lesions typically form multiple abscesses with draining sinus tracts. On closer inspection, the abscesses may contain yellow granules resembling grains of sand termed “sulfur granules”. Although the sulfurous

Compare and contrast the clinical types of PID

Acute PID refers to infections that last less than 30 days in duration. Most infections are caused by sexually transmitted pathogens, whereas others occur in the puerperium.

What is the etiopathogenesis of PID?

Acute PID is an infection with a shorter duration. The vast majority (85%) of these infections are sexually transmitted and spread through the ascending route from the lower reproductive system to the pelvic area. Infection commonly occurs in sexually active young women, with the most frequent causative agents being N. gonorrhoeae and C. trachomatis. A minority of infections occur in the puerperium, tend to be poly-microbial, and include bacterial vaginosis pathogens (Gardnerella, Peptostreptococcus species, and Bacteroides species). Chronic PID is an infection of longer duration and is associated with Mycobacterium tuberculosis or Actinomyces species. Fungal and parasitic infections are rare causes of PID. Fungal infections include those caused by Cryptococcus and Blastomyces, and parasitic infections include those caused by Schistosoma, Enterobius, Toxoplasma gondii, and Entamoeba histolytica.

Gonococcal infections involve the mucosal surfaces, commencing from the endocervical mucosa and extending to the uterine endometrium and spreading to the tubo-ovarian region. Non-gonococcal infections ascend to the uterus and do not show mucosal inflammation because they are likely to spread through lymphatic and venous channels. Bacterial vaginosis pathogens produce enzymes that degrade cervical mucus, and antibacterial proteins disrupt the cervical barrier, resulting in tubo-ovarian spread.

Immunocompromised patients are predisposed to opportunistic fungal infections that may affect the reproductive tract. Cryptococcus and Blastomyces may cause granulomatous inflammation making it difficult to distinguish from tuberculosis. Serology, culture, and special stains are often necessary to confirm a diagnosis.

Genitourinary infections caused by Schistosoma are acquired through travel to endemic countries and contact with contaminated water. Perianal parasites, such as Enterobius vermicularis migrate, causing vulvovaginitis and, rarely, upper genital infections. Toxoplasmosis is a protozoal parasitic infection caused by the accidental ingestion of oocysts from cat feces or eating raw meat. Toxoplasma induces endometritis and predisposes neonates to congenital transplacental spread during pregnancy.

Acute PID refers to infections that last less than 30 days in duration. Most infections are caused by sexually transmitted pathogens, whereas others occur in the puerperium.

Fig. 2. Section of ovary stained with H&E. Microscopy (10X) shows Actinomyces bacterial colonies (A) displaying Spindel-Hoeppli phenomenon (S) surrounded by suppurative inflammation with abundant polymorphonuclear neutrophils (PMN).

Fig. 3. This image depicts an inflamed uterus and ovary removed due to the presence of an ovarian abscess in a case of pelvic inflammatory disease (PID) and caused by an undisclosed anaerobic bacterium. (Image attribution: Image # 17,605, public health image library, CDC/Jim Pledger. https://phil.cdc.gov/default.aspx permission as an open-access source.)
often mistaken for gynecological tumors. Bladder involvement can mimic surgery, or a foreign body.3,11,14

...tissue, which gives the lesion a hard consistency.12 This leads to mandibular... when the mucosal barrier breaks down. The infection is further facilitated by bacterial vaginosis pathogens can induce an anaerobic environment that favors the growth of Actinomyces.14

The “Splendore-Hoeppli” phenomenon provides a resistance mechanism to evade the host immune system and inhibit phagocytosis.10,13

How do Actinomyces overcome host defenses after entry?

As Actinomyces is an opportunistic pathogen, progression to a clinical infection requires a breach of the mucosal barrier caused by trauma, surgery, or a foreign body.3,11,14

...Companion bacteria produce toxins, weaken host defenses, reduce oxygen tension, and facilitate Actinomyces infection.13 In the reproductive tract, an infection caused by bacterial vaginosis pathogens and the associated loss of normal vaginal lactobacilli elevates the pH, resulting in less acidity6,8 and creating an anaerobic environment favoring the growth of Actinomyces.14

The “Splendore-Hoeppli” phenomenon provides a resistance mechanism to evade the host immune system and inhibit phagocytosis.10,13

What are the predisposing risk factors for acquiring Actinomyces infection?

...Actinomyces is an organism with low virulence and becomes invasive when the mucosal barrier breaks down. The infection is further facilitated by companion bacteria. Cervicofacial actinomycosis is caused by odontogenic infections. Poor dental hygiene, dental caries, dental surgery, and systemic illnesses, such as diabetes, are predisposing factors for this infection.10,13 Pulmonary actinomycosis results mainly from the aspiration of gastrointestinal secretions. Predisposing factors for these infections include alcohol abuse and seizure disorders. Chronic lung diseases, such as tuberculosis and obstructive and restrictive lung diseases, damage the mucosal defenses, predisposing Actinomyces infection. In women, IUD use increases the risk of pelvic actinomycosis. Prior surgery for appendicitis and colonic diverticulitis may be a risk factor for gastrointestinal actinomycosis. Immunosuppressive conditions, such as HIV infection, organ transplantation, treatment with biologics, and malignancy, are other risk factors.10,13

Describe the pathogenesis of pelvic actinomycosis infection

Pelvic actinomycosis occurs predominantly in women using IUDs.3,11,14,16 Studies have shown that Actinomyces-like organisms reside in the cervix, vulva, and perineum.17 IUD insertion results in a small portion of the attached strings to normally protrude through the ectocervix (Fig. 4). These wires or strings may aid microbial growth and cause ascending infection.14 IUD insertion traumatizes the epithelium, disrupts the mucosal barrier, and causes erosion, which may predispose to Actinomyces invasion.10 In addition, pre-existing infection by bacterial vaginosis pathogens can induce an anaerobic environment that favors the growth of Actinomyces14. IUD insertion also alters carbohydrate
studies have recommended changing the IUD every three years to prevent actinomycosis.3,15 Therefore, the diagnosis of pelvic actinomycosis is often made postoperatively.11,14

Women who choose IUD as a form of contraception should be informed of the low potential risk of actinomycosis.11 Although little data are available, the risk of future symptomatic infection is estimated to be less than 1/1000.11 Some studies have recommended changing the IUD every three–five years.10,14 Laboratory tests, such as a complete blood count, are likely to show leukocytosis with neutrophilia. Levels of inflammatory markers, such as ESR and CRP, are likely to be elevated. Levels of tumor marker CA-125 may be slightly elevated, making it difficult to rule out ovarian tumors.2,4,10 Pap smears may detect Actinomyces-like organisms but cannot differentiate between colonization and infection.10,13

CT, ultrasound, and other imaging studies are useful in detecting pelvic masses but may be difficult for distinguishing between chronic inflammatory conditions and cancer. These can detect lymphadenopathy as seen in 50% of patients with pelvic actinomycosis.12,13 They are also helpful for retrieving guided biopsies or aspiration.3,10,14

The gold standard for the diagnosis of actinomycosis is a histopathological examination and bacterial culture from a tissue biopsy or aspirated material. Bacterial culture is a slow process and may take 15–20 days. Strict anaerobic processing is also required. When grown, colonies of Actinomyces israelii appear like a “molar tooth”10,12 (Fig. 5).

Histological evaluation of the infected tissue may show suppurrative and granulomatous inflammation along with granulation tissue and Actinomyces bacterial colonies displaying the Splendore-Hoeppli phenomenon14 (Fig. 2). Gram staining shows the presence of filamentous gram-positive rods (Fig. 6). Bacterial colonies can also be visualized using immunofluorescence techniques10 (Fig. 7). Molecular techniques using 16S rRNA sequencing are further useful methods for identification.10,14

**How is pelvic actinomycosis treated?**

Actinomyces spp. are sensitive to penicillin G and beta-lactams. Other antibiotics, such as clindamycin, macrolides, tetracycline, and doxycycline, are also effective and used in patients allergic to penicillin or displaying antibiotic resistance. IUDs should also be removed in patients with IUD-associated pelvic actinomycosis. The usual length of treatment is 6–12 months.10,13,15 Patients in an uncomplicated clinical course may be managed with antibiotics to avoid surgical intervention and maintain future fertility.14 Surgical intervention supplemented with antibiotics offers a cure for the most complicated cases.10,17 Therapy may be shortened to three months if the patient undergoes surgical removal of the infected site.10,13,15

**What are the complications of PID?**

Acute PID caused by gonorrhea is associated with severe inflammation spreading to the fallopian tubes (acute salpingitis) and ovaries...
This can account for chronic pelvic pain and, in severe cases, may cause ureteral or bowel obstruction.7,18

The patient is successfully treated with a three-month course of antibiotics after surgery and is doing well thereafter. She is advised to follow-up and is recommended to undergo hormone replacement therapy. With the elevation of inflammatory markers and IUD use, the awareness of the variation in CA-125 levels in pre- and post-menopausal women and investigation with ultrasound-guided fine-needle aspiration cytology could potentially avoid the need for surgery.

**Teaching points:**

- Pelvic inflammatory disease (PID) is an infectious and inflammatory disorder of the female upper reproductive system.
- Acute PID is commonly caused by *N. gonorrhoeae* and *C. trachomatis*, which are sexually transmitted via an ascending route of infection from the lower reproductive system.
- PID caused by fungal and parasitic infections is usually seen in immunocompromised hosts and after travels to endemic countries.
- *Actinomyces* is an opportunistic gram-positive bacteria and a rare cause of chronic PID.
- Progression to clinical infection requires a breach of the mucosal barrier, which may be caused by trauma, surgery, or a foreign body.
- Pelvic actinomycosis should be considered a differential diagnosis in patients with an ovarian mass, despite the absence of clinical and laboratory evidence of inflammation.
- Pelvic actinomycosis is an insidious disease that is often mistaken for malignancy, and it should be viewed with a high index of suspicion in any patient harboring an IUD that exceeds four years of duration.
- The gold standard for diagnosis is a histopathological examination and bacterial culture from a tissue biopsy or aspirated material.
- Most patients in the reproductive age group with uncomplicated disease courses are treated conservatively with antibiotics to avoid invasive surgery and retain fertility.

**Declaration of competing interest**

The author declares no potential conflicts of interest.

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