

Aspergillus and cervicovaginal papanicolaou smear: a review

Abstract

Background: *Aspergillus* is a ubiquitous fungus known to cause *aspergillosis* in immunocompromised patients. The involvement of female genital tract by this fungus is rarely described. Reports of finding *Aspergillus* in cervicovaginal smears have appeared.

Method: A comprehensive literature search was conducted from the websites of Pubmed Central, the US National Library of Medicine's digital archive of life sciences literature (<http://www.pubmedcentral.nih.gov>), and Google Scholar. All articles displayed using the search words "*Aspergillus* and cervicovaginal smear" were included in this review. Books that published relevant articles in this field were also considered.

Result: The *Aspergillus* is identified in smears by conidiophores and characteristic hyphae against a background of squamous cells and inflammatory cells. It should be confirmed and characterized by culture.

Conclusion: Contamination should be ruled out in all the cases of *Aspergillus* in cervicovaginal Papanicolaou smear. Treatment should be done to prevent serious consequences in the patients if pelvic surgery is done and in a potential situation when patient develops an immunocompromised state in future.

Keywords: *Aspergillus*, aspergillosis, cervicovaginal smear, papanicolaou smear

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Anand Kumar Verma, Onkar Kaur

Department of Pathology, Employees State Insurance (ESI)
Postgraduate Institute of Medical Sciences India

Correspondence: Anand Kumar Verma, Department of Pathology, Employees State Insurance (ESI) Postgraduate Institute of Medical Sciences and Research and ESI Model Hospital, Basaidarapur, New Delhi 110015, India, Email anandverma1961@gmail.com

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Introduction

Ubiquitous is the term used to describe the fungus *Aspergillus*. It is one of the oldest named genera of fungi and has been subject of medical interest for more than two and half centuries.¹ All *aspergillus* related diseases are called aspergillosis.^{2,3} Cervicovaginal smear is an important and common investigation in gynecological practice. It was conceived by Papanicolaou and Traut as a tool to detect precancerous as well as cancerous lesions of squamous cell origin.⁴ However, it also provides information about some non-neoplastic lesions including infections of lower genital tract.⁵ In recent times, *Aspergillus* has been found to colonize vagina and is increasingly being identified in cervicovaginal smear.⁶⁻⁹

Aspergillus: a brief history

Aspergillus received its name from Micheli in 1729. Pier Antonio Micheli was a famous botanist as well as a Catholic Priest. His *Nova Plantarum Genera* of 1729 was a milestone in the study of fungi. On viewing the spore-bearing structure of the fungus under the microscope, Micheli was reminded of a device called aspergillum used by the Roman Catholic clergy to sprinkle holy water during a part of the liturgy called the *asperges*.¹ The genus *Aspergillus* has more than 250 species.¹⁰ About 40 of these have been reported as human pathogen but majority of case are associated with one species i.e. *Aspergillus fumigatus*.¹¹ Other common species implicated are *Aspergillus flavus* and *Aspergillus Niger*.¹²

Aspergillus: the basic structure

Filamentous fungi (molds) are ancient lineages that have existed

for approximately 1 billion years.³ They were referred as white, yellow, green red or black molds. The advent of the microscope brought out their structure. The aspergillum-like spore-bearing structure, also called fruiting body, is the most important microscopic character used in defining members of the genus *Aspergillus*. During mycelial differentiation certain cells enlarge, develop a heavy cell wall and form 'T' or 'L' shaped 'foot cells', which are not separate cells and that produce a single conidiophore perpendicular to the long axis of the cell. The erect hypha branch developing from the foot cell is the conidiophore, which enlarges at its apex to form a rounded, elliptical or club shaped vesicle. The fertile area of the vesicle gives rise to a layer of cells called phialides (earlier called sterigmata) that produce long chains of mitotic spores called conidia or conidiospores. The size and arrangement of the conidial heads, size and contours of vesicle, arrangement of phialides as well as the color, size and length of the spores they bear are important identifying characteristics.¹ *Aspergillus fumigatus*, the commonest human pathogenic fungus microscopically shows septate hyphae 3-6 μ in size branched at 45° angles with conidial heads composed of a vesicle, phialides and conidial chains.^{11,13}

Aspergillus and aspergillosis

Aspergillosis is the name given to all diseases caused by the growth of any member of the genus on a living host. These diseases are a spectrum of disorders of immunity. It occurs in highly immunocompromised person or in those who have poorly controlled inflammatory response to fungal hyphae.³ Typically only patients with compromised immune system or who suffer from other lung conditions (cystic fibrosis, chronic obstructive pulmonary disease and severe asthma) are susceptible to aspergillosis. Patients with diabetes,

cancer notably leukemia and lymphoma, those on chemotherapy, chronic steroid therapy, transplant recipients, patients with HIV, and chronic granulomatous disease are susceptible hosts.^{14,15} Lung is the commonest site of involvement. Other organs which are known to be affected by *Aspergillus* are skin, brain, bone, eye, paranasal sinuses, ear, endocardium, thyroid, liver, gastrointestinal and urinary tract.^{2,13} The female genital tract is rarely involved by this fungus.¹⁶⁻¹⁸

Cervicovaginal smears and fungus

The 2014 Bethesda system of reporting cervical cytology includes fungal organisms morphologically consistent with *Candida* spp. No other fungus including *Aspergillus* has been mentioned because of their rarity.⁵ Apart from *Candida albicans*, fungal pathology is rarely seen in cervicovaginal smears. Most reported cases of cervicovaginal smears with opportunistic fungus include *Blastomyces dermatitidis*, *Coccidioides immitis*, *Cryptococcus neoformans* and *Mucor* with very few cases of *Aspergillus* spp.

Cervicovaginal colonization by aspergillus and its significance

Large studies showing prevalence of cervicovaginal colonization by *Aspergillus* are rare. In a community based house to house survey using cluster sampling, 1344 married women from both urban and rural area of Egypt were studied to look for reproductive tract infections. 7.4% of these women had *Aspergillus*.¹⁹ In a hospital based study, the prevalence of *Aspergillus* in non-immunocompromised women was 0.6%.¹⁴ The patients had persistent vaginal discharge, itching and irritation. There were signs of vulvitis in form erythema, scaling or folliculitis. The vestibules were inflamed and showed fissure formation. Vagina was inflamed with various degrees of ectasia and discharge. No significant collateral infection was observed. Narasimha et al.³ found 0.15% cases of *Aspergillus* in a retrospective analysis of 1252 subjects having complaints of vaginal discharge, backache, dyspareunia, dysuria or post-coital bleeding.²⁰

There is possibility of increased morbidity in case of patients with fungal colonization undergoes abdominal or vaginal hysterectomy, pelvic floor reconstruction or any vaginal operation for urinary incontinence. The development of any immunocompromised state may lead to systemic aspergillosis.^{14,15}

Morphology of aspergillus in cervicovaginal smears

Aspergillus in low magnification appears a collection of numerous intermeshed fungal hyphae and spores. At higher magnification, abundant fruiting bodies are also seen. Hyphae are uniform 4-6 μ in diameter, hyaline and septate, with parallel walls and acute angle branching.²¹ The fruiting bodies were composed of long conidiophores with club shaped vesicles covered with phialides. These are capped by long chains of spherical conidia. These fungal structures are mixed variably with squamous cells, transformation zone cells as well as inflammatory cells. In presence of dense inflammation the structure of fungus is difficult to visualize (Figure 2 & Figure 3).

Diseases associated with Aspergillus in cervicovaginal smears

Deb and Srivastava reported a case in post menopausal female with pelvic inflammatory disease. There was a complaint of foul smelling discharge per vaginum and pain in hypogastrium. On examination unhealthy cervix was found.

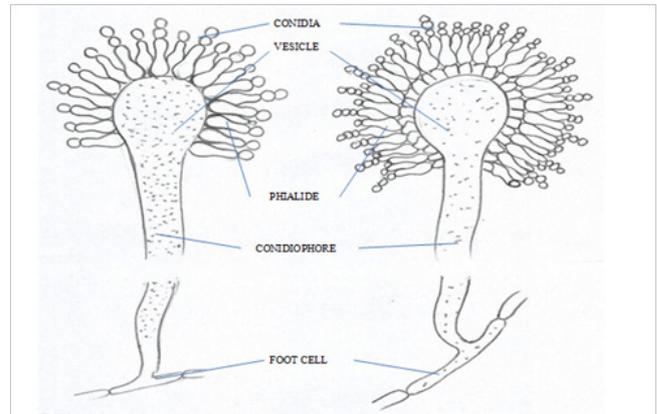


Figure 1 The basic structure of *Aspergillus* Spp. (Adapted from "Monograph on *Aspergillus* and Aspergillosis in man, animals and birds: A guide for classification and identification of aspergilli, diseases caused by them, diagnosis and treatment.")

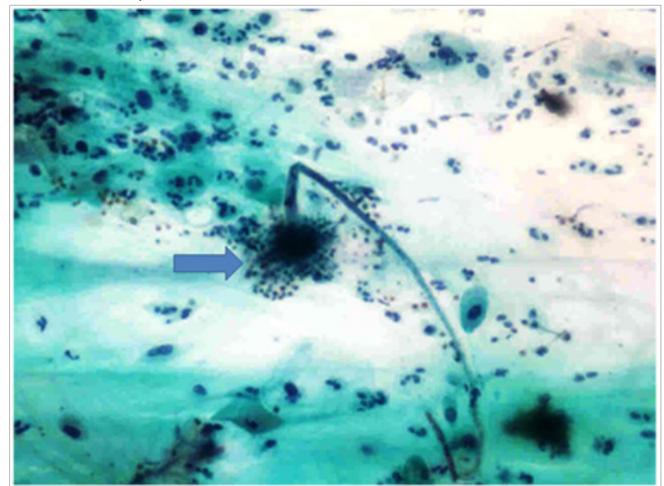


Figure 2 Photomicrograph of fruiting body (conidiophore) of *Aspergillus*. Multiple conidia are identified (Papanicolaou stain 400 \times). Background shows squamous cells and neutrophils.

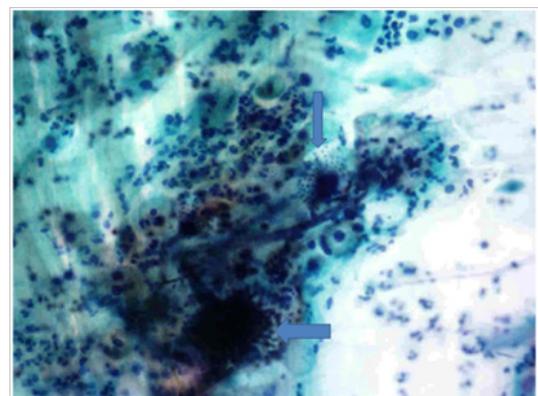


Figure 3 Photomicrograph multiple conidiophores of *Aspergillus* which are entangled in inflammatory cells (Papanicolaou stain 200 \times).

Smears showed the features of severe inflammation, along with fungal structures with fruiting bodies consistent with the presence of *Aspergillus spp* mixed with epithelial cells which were negative for intraepithelial/malignancy. Repeat, smear after treatment of pelvic inflammatory disease in addition showed high grade squamous intraepithelial lesion. Four quadrant biopsies also showed presence of squamous cell carcinoma.²² Gupta et al have also reported a case of concomitant *aspergillus* infection and squamous cell carcinoma.²³ Mane et al have reported a case of concomitant *Candida* and *Aspergillus* infection.²⁴

Aspergillus as contaminant in cervicovaginal papanicolaou smears

Finding fruiting bodies and hyphae of *aspergillus* in a routine cervicovaginal pap smear is a rare occurrence. When encountered it is important to distinguish between a true infection and contamination.^{25–28} A contaminated smear overrules the toxic antifungal therapy and undue follow-up, whereas true infection requires careful study of immune status and prompt therapy.⁶

Aspergillus is an environmental fungus transmitted by airborne conidia. It is able to grow over a temperature wide range from below 20°C up to 50°C and grows well over 40°C. It grows well in vegetable matter.¹³ Dirty air conditioning units with poor ventilation system are potential source of contamination.¹⁵ Damp areas of room, in cellars and basement, drain pipes, food stores and kitchen are all sources of *Aspergillus* contamination.^{29,30}

The cervicovaginal smear collection and its processing till it is interpreted involve various steps which may potentially produce a contamination in ill controlled environment.³¹ While visualizing the cervix, the speculum and water used to facilitate its insertion may be contaminated.²⁵ The collection devices which include endocervical or broom type brushes; and spatula both wooden and plastic are prone to contamination if not stored properly especially in low turnover hospital settings. The glass slides on which smear are made also get contaminated. Laboratory solutions and water used for staining may also contribute. All these source of contamination should be ruled out diligently in each case of cervicovaginal smear with fungal components.⁶ Culturing and characterization of fungus before initiating therapy is important to avoid unnecessary treatment due to contaminant fungus. However, growth in culture also needs to be interpreted with caution because of ubiquitous nature of conidial spores.³²

Conclusion

The infection of female genital tract by *Aspergillus* is rare. There presence in the cervicovaginal Papanicolaou smear should prompt the clinician to rule out contamination and treat the patient after culturing the fungus. This will prevent serious consequences in the patients if pelvic surgery is done and in a potential situation when patient develops an immunocompromised state.

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Conflict of interest

The author declares no conflict of interest.

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