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Corresponding Author
Dipak Kumar Dhar,
Department of Medical Education, NMC Regional Center for Medical Education Technologies, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Jolly Grant, Dehradun, Uttarakhand, India
dhardkd90@gmail.com

Author Designation
[1]Medical Officer
[2]Professor and Head
[3]Associate Professor

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The Mycobiome of Nasal Polyps in Immunocompetent Individuals: A Case Series

[1]Mousumi Paul, [2]Tapan Majumder and [3]Dipak Kumar Dhar

[1]Tripura Health Services, Indira Gandhi Memorial Hospital, Agartala, Tripura, India
[2]Department of Microbiology, Agartala Government Medical College and GB Pant Hospital, Agartala, Tripura (West), India
[3]Department of Medical Education, NMC Regional Center for Medical Education Technologies, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Jolly Grant, Dehradun, Uttarakhand, India

ABSTRACT
Nasal polyps are benign growths within the nasal passages, often associated with chronic inflammation. While various factors contribute to their development, the exact etiology remains unclear. Fungal infections have been linked to nasal polyposis, primarily in immunocompromised individuals. Here we present description of three cases where the same was found in immunocompetent individuals. This case series describes three immunocompetent individuals with severe nasal polyposis. A 40-year-old woman presented with a three-year history of nasal blockage, frontal headache, and intermittent right-sided nasal discharge. Microscopic examination and fungal culture of the resected polyp revealed a mixed infection with Bipolarissp and Alternariasp. A 19-year-old man presented with a six-month history of left-sided nasal blockage, facial pain and anosmia. Fungal culture identified Aspergillus niger in the resected polyp. A 65-year-old man presented with a nine-month history of right-sided nasal blockage and occasional bleeding. Fungal culture revealed Rhizopus species in the resected polyp. These cases demonstrate the importance of considering fungal infections in the etiology of nasal polyps, even in immunocompetent individuals. The presence of unusual fungal pathogens highlights the need for thorough microbiological investigations in patients with nasal polyposis, as this information can guide post-surgical management and potentially improve patient outcomes.

INTRODUCTION

Nasal polyps are soft, painless, benign growths on the lining of nasal passages or sinuses. They are hyperplastic outgrowths usually associated with some form of inflammation. Till date, no specific genetic or environmental factors have been strongly linked to the development of this disorder[1]. They result from chronic inflammation and are often associated with asthma, recurring infection, allergies, drug sensitivity like aspirin or certain immune disorders, with a considerable tendency of recurrence[2,3]. Pathologically, polyps resulting as a consequence of such chronic inflammatory conditions in the nose and nasal sinuses are characterized by stromal edema and variable cellular infiltrate[4,5]. Clinical manifestations depend on the size of polyps, its number and it ranges from asymptomatic to nasal blockage, breathing difficulty, loss of smell sensation and recurrent infections. Because these polyps may block nasal airways and create breathing difficulties or inhibit proper drainage of the sinus cavities, they can cause stagnation of secretions, leading to sinusitis. An increase in size of polyp may exert pressure effects on the adjacent bones and cause destruction of nasal and other facial bones and causing other complications[4,5]. Infections of various etiologies have been suggested as possible factors along with other reasons like environmental factors like pollution in development of chronic inflammation and developing nasal polyposis[6]. The role of fungi in polyposis remains present but quite elusive. An association between polyposis and fungal cultures has been known for some time, but the exact mechanism still remains unclear[7-9]. Most of fungal etiologies appear in conditions of low immunity. In recent times, some reports have suggested that in cases of severe nasal polyposis, fungal rhinosinusitis could be a causative factor as isolated from resected specimens both on microbiological and histopathological mechanisms[9]. There is about 1.5-5 million species of fungi. Some of them form spores that we inhale on a daily basis (e.g. Aspergillus species), while others co-exist with us as human commensal organisms (e.g. Candidasp). Fungal spores are ubiquitous in the environment. They can gain access to the body through various portals, but entry through inhaled air is common. The spores may become saprophytic within a host and multiply. A robust immunity prevents the development of fungal disease. Most of the disease-causing fungi are opportunistic pathogens which implies they have the potential of causing disease processes under certain circumstances like when the effectiveness of the immune system is weakened or suppressed[10]. The most common fungal infections that can affect immunocompetent individuals include histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, sporotrichosis, cryptococcosis and aspergillosis[11]. In this paper, we present three cases who presented with severe nasal polyposis, all of whom were immunocompetent and yet when the resected polyps were studied by mycological and histopathological methods, fungi were isolated. As outlined above, fungal aetiology although documented, is not the commonest cause of nasal polyposis. While fungal infections are expected in immunocompromised states, the presence of fungal infections, especially in patients without impaired immunity make them interesting. Furthermore, in each of them, the isolated fungi were unusual for immunocompetent patients. In this series, mixed infection with Alternaria and Bipolarisspecies, Aspergillus niger, Rhizopus species were isolated as the causative agents.

Case no. 1: A 40 years old female patient presented to ENT OPD of Agartala Government Medical College and GB Pant Hospital with frontal headache, right-sided nasal discharge occasionally and chronic nasal blockage for last 3 years for which she was taking steroid inhaler intermittently. She did not have any history of fever or any systemic condition suggestive of impaired immunity. Endoscopic examination of the nose and paranasal sinuses was done, followed by a computed tomographic scan of the paranasal sinuses. It revealed a hyperattenuating mass in the right frontal sinus. Her routine haematological examination was found to be unremarkable, with cell counts well within the normal limits. Once the diagnosis was clinched, the mass was removed by unilateral endoscopic surgery and the sinus was irrigated with normal saline and antifungal solution. The mass was sent to the microbiology department for microbiological confirmation. She was discharged from hospital after 5 days with oral medications and was asked for follow-up after 2 weeks.

Macroscopic Examination: A tissue section measuring around 2.5 cm by 2.5 cm, brownish in colour, fleshy in appearance and consistency was received in normal saline. The tissue was ground and the material was subjected to gram-staining, Ziehl-Neelsen (ZN) staining, Potassium Hydroxide (KOH) mount and aerobic bacteriological culture and fungal culture. For bacteriological culture, blood agar and MacConkey agar was inoculated and incubated aerobically at 37°C. Two pairs of Sabouraud Dextrose Agar (SDA) tubes (one with antibiotic and other without antibiotic) were inoculated with the material and one pair of those tubes was incubated at 25°C and other pair at 37°C.

Microscopic Examination:

1. **Gram Staining:** 2-5 pus cells were seen per HPF, but no organism could be seen.

2. **ZN Staining:** No acid fast structures were found.
3. **KOH Mount (20%):** Narrow septate, dematicious and hyaline fungal-hyphal like structures were seen.
4. **Aerobic Bacteriological Culture:** After 48 hours of incubation, no growth was observed on culture.
5. **Fungal Culture:** On 4th day, the SDA tube incubated at 25°C with out antibiotic showed rapid, profuse growth. It was characterized by obverse, side-woolly, cottony colony which was whitish in colour interspersed with slight black-colour as shown in (Fig. 1). Subsequently, Lactophenol Cotton Blue (LPCB) mount was performed from the colony and it showed a mixture of narrow septate hyaline fungal hyphae with sickle-shaped, large macroconidia and dematicious, septate macroconidia. There was no growth in the tubes incubated at 37°C. For further confirmation, slide culture test was performed and it was diagnosed morphologically as a mixed infection of Bipolaris sp. and Alternaria sp. as shown in (Fig. 2) and (Fig 3). Mixed mould infection was also detected on histopathology.

Case no. 2: A 19 years old male patient presented to the ENT OPD with symptoms of left-sided nasal blockage, mild to moderate grade pain on the left side of the face, localised diffusely over the cheek and headache for the last 6 months. Over the last one month, he also started suffering from anosmia, insidious in onset and gradually progressive. He was clinically provisionally diagnosed as a case of left sided maxillary

Fig. 1: SDA Tube Showing Woolly, Cottony Flat, Whitish with Slightly Black Coloured Colony (Obverse)

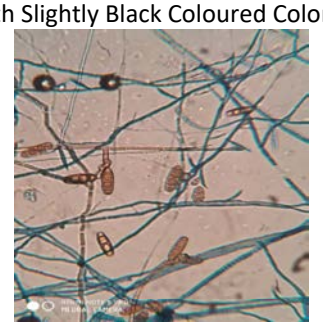

Fig. 2: LPCB Mount Showing Hyaline Hyphae and Dematicious Macroconidium of Bipolaris sp. and Alternaria sp

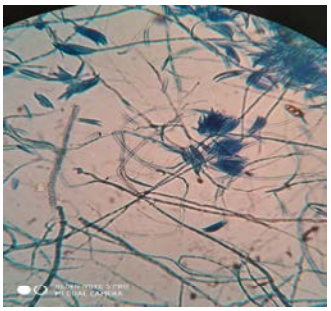

Fig. 3: LPCB Mount (Slide Culture) Showing Hyaline Alternaria and Dematicious Bipolaris Fungi

rhinosinusitis which was subsequently confirmed on radiological imaging by computed tomography. There was no history suggestive of immunocompromised sates. The systemic examination was within normal limits. And the cell counts on complete hemogram were also unremarkable. Functional Endoscopic Sinus Surgery (FESS) was done and a fleshy mass with dimensions of 3.5 cm by 2. cm approximately was removed. For microscopic confirmation, it was sent to microbiology and pathology departments. After the removal of that mass, patient was treated with oral antimicrobials. He was discharged after 5 days and was asked to attend ENT OPD with the reports after 15 days for follow up.

Macroscopic Examination: A tissue section measuring approximately 3.5 cm X 2.5 cm, fleshy mass, whitish in colour was received in normal saline. The tissue was ground and the material was subjected to gram-staining, Ziehl-Neelsen (ZN) staining, Potassium Hydroxide (KOH) mount and aerobic bacteriological culture and fungal culture. For bacteriological culture, blood agar and MacConkey agar was inoculated and incubated aerobically at 37°C. Two pairs of Sabouraud Dextrose Agar (SDA) tubes (one with antibiotic and other without antibiotic) were inoculated with the material and one pair of those tubes was incubated at 25°C and other pair at 37°C.

Microscopic Examination:

- **Gram Staining:** 2-5 pus cells were seen per HPF. And narrow septate fungal hyphae were also seen.
- **ZN Staining:** No acid fast structures were found.
- **KOH Mount (20%):** Narrow septate hyaline fungal hyphal like structures were seen as shown in (Fig.4).
- **Aerobic Bacteriological Culture:** After 48 hours of incubation, no organism grew on culture.
- **Fungal Culture:** On 4th day of incubation, the SDA tubes incubated at 25°C, both with and without antibiotic showed profuse growth characterized by rapid growth, obverse side- cottony granular black coloured, reverse-non pigmented colony as

depicted in (Fig. 5). Following this, Lactophenol Cotton Blue (LPCB) mount was performed from the colony. It showed narrow septate fungal hyphae with conidiophores and black-coloured conidia arising from entire vesicle as shown in (Fig. 6). Also, there was no growth in the SDA tubes that were incubated at 37°C. It was diagnosed as Aspergillus group of fungus. For further speciation, slide culture test was performed and it was diagnosed morphologically as AspergillusNiger.

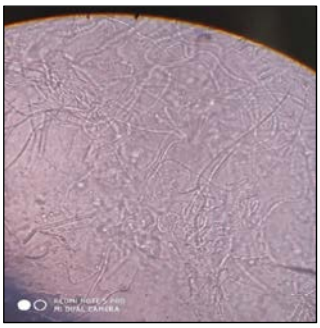

Fig. 4: KOH Mount from the Polyp Mass Showing Multiple Narrow, Hyaline, Fungal Hyphae

Fig. 5: SDA Tube Showing Black Granular Cottony Surface (Obverse) of Aspergillus Niger

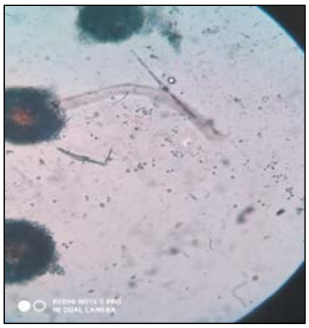

Fig. 6: LPCB Mount is Showing Black Coloured Conidia Arising from Entire Vesicle and Conidiophores

The final diagnosis on the basis of history, clinical findings, radiological investigation, microbiological and histopathological examination was made as a case of nasal polyp caused by apergillus Niger in an immune-competent adult.

Case no. 3: A 65 years old male patient presented to the ENT OPD, Agartala Government Medical College and GB Pant Hospital with the complaints of headache and right-sided nasal blockage for the last 9 months. It was also accompanied with and occasional intermittent nasal bleeding. There was a history of hypertension diagnosed about three years back for which he is on medication. There was no history of intake of any other medications. There was no condition suggestive of acute or chronic immunosuppression. On clinical examination, he was provisionally diagnosed as a case of right-sided maxillary polyp with hypertension. Computed Tomographic scan of nose and paranasal sinus showed right-sided unilateral anterior opacities with maxillary bone erosion and widening of maxillary ostium. Once the diagnosis was clinched, endoscopic sinus surgery was performed. The maxillary sinus was found to be filled with thick, brown secretions and a mass of 2 cm x 6 cm was surgically removed. The maxillary sinus was irrigated with normal saline following removal of that mass. It was sent to microbiology and pathology departments in halves for further investigations as per hospital protocol. After the removal of that mass, patient was treated with antimicrobials and discharged after 5 days. He was asked to attend ENT OPD with reports after 15 days for follow up.

Macroscopic Examination: A tissue section measuring around 1.5 cm x 3 cm, fleshy and whitish in colour was received in normal saline. On macroscopic examination there were no granules over its surface. The tissue was ground and the material was subjected to gram-staining, Ziehl-Neelsen (ZN) staining, Potassium Hydroxide (KOH) mount and aerobic bacteriological culture and fungal culture. For bacteriological culture, blood agar and MacConkey agar was inoculated and incubated aerobically at 37°C. Two pairs of Sabouraud Dextrose Agar (SDA) tubes (one with antibiotic and other without antibiotic) were inoculated with the material and one pair of those tubes was incubated at 25°C and other pair at 37°C.

Microscopic Examination:

- **Gram Staining:** 2-5 pus cells were seen per HPF, but no organism could be seen.
- **ZN Staining:** No acid fast structures were found.
- **KOH Mount (20%):** Broad aseptate hyphal like structure could be seen.
- **Aerobic Bacteriological Culture:** After 48 hours of incubation, no growth was observed on culture.
- **Fungal Culture:** On 3rd day of incubation, the SDA tube incubated at 25°C without antibiotic showed profuse growth characterized by rapid growth, obverse side- cottony, woolly greyish-white colony suspended in air and reverse, non-pigmented as shown in (Fig. 7). After that, Lactophenol Cotton Blue (LPCB) mount was performed from the colony and it showed broad aseptate hyphae with

sporangiophore, sporangium containing spores and nodal rhizoids, depicted in (Fig. 8 and 9). There was no growth in the SDA tube with antibiotic incubated at 25°C or in the tubes incubated at 37°C. It was diagnosed as zygomycetes group of fungi. For further speciation, slide culture test was performed and it was diagnosed morphologically as Rhizopus species.

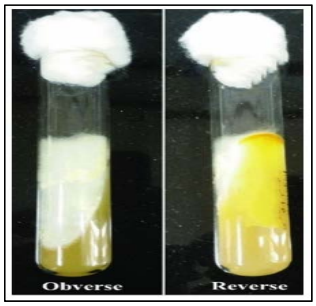

Fig. 7: SDA Tube without Antibiotics Showing Profuse Cotton-Woolly Growth on Obverse Side (on Day 3 of Incubation at 25°C)

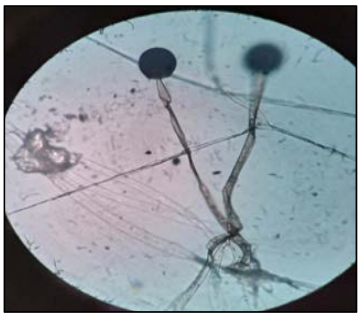

Fig. 8: LPCB Mount of Colony Showing Broad Aseptate Hyphae with Branched Sporangiophore, Sporangium Containing Spores and Nodal Rhizoids (400X)

Fig. 9: LPCB Mount of Colony Showings Porangiophore, Sporangium and Nodal Rhizoids (400X)

The final diagnosis was made as a case of nasal polyp caused by Rhizopus species of fungus in an immune-competent adult. Nasal polyps are the most common non-cancerous growths of the nasal cavity, affecting around 1-4 percent of the population[4]. Their clinical manifestations are directly related to their location and size and in extreme cases there may be orbital and even intracranial complications. As outlined in the beginning, the exact causative agent is not known conclusively. But several factors ranging from microorganisms to environmental pollution have been suggested by researchers. The common underlying feature in all of them is a state of chronic inflammation in the nasal cavity[2,4]. Fungal-caused nasal polyposis have been reported in literature, but what makes our cases unique is that all the three patients were immunocompetent and unlikely to suffer from a fungal disease. And the organisms isolated were unusual for fungi in immunocompetent states. Out of the Aspergillus sp. reported in similar scenarios in medical literature, Aspergillus flavus is the commonly isolated organism[9]. However in second case in our case-series, the isolated fungus Aspergillus niger. A probable mechanism which might have led to this state could be an IgE-mediated hypersensitivity to fungal colonization of the paranasal sinus mucosa as seen in chronic rhinosinusitis. According to the recent concepts, inhaled fungal elements become entrapped in the mucus lining of the nasal cavity and sinuses attracting migration of eosinophils from the respiratory tract into the lumen. It has been proposed that subsequently eosinophils cluster around and attack the fungal elements in an immune reaction[12-15]. Although, the primary management of nasal polyps includes surgical resection with or without medical management and that will not be altered by microbiological diagnosis, the isolation and identification of fungal etiology if present, could drastically alter the course of the patient post-surgical resection as medical management with fungal eradication can improve patient outcomes and avoid recurrence in the long-run.

CONCLUSION

The present case-series shows that it is important to look for the presence of fungus in nasal polyps irrespective of the state of immunity of the patients. Isolation of fungal etiology necessitates administration of anti-fungal therapy for benefit patient outcomes and preventing recurrence.

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