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Original Research Article

Histomorphological Spectrum of Fungal Lesions in the Sinonasal Tract in a Tertiary Care Hospital

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Abstract

The head and neck area is the most complex area of the human body, with its most physical connections to the outside environment. So it plays host to a variety of infections. Sinonasal tract fungal infections are not uncommon and the surgical pathologist is concerned with establishing a correct etiological diagnosis because many of the infectious fungal masses are confused with neoplasms both clinically and radiologically. So this study was aimed to identify the histomorphological type of fungal infections in the sinonasal tract and their prevalence according to various clinical parameters. This was a retrospective study carried out in the Department of Pathology, Karpaga Vinayaga Institute of Medical Sciences for a period of 3 years (Feb 2016 to Feb 2019) and all the Sinonasal tract lesions morphologically diagnosed to have fungal infections were included in this study**.** During the study period, Out of 11,301 total histopathology specimens received, 40 cases were diagnosed with sinonasal fungal infections (0.35%). Of these, 77.5% were males, 22.5% were females with male preponderance. The most common type of fungal infection was Aspergillosis (14 cases), followed by Mucormycosis (11cases). The most common site of infection in the sinonasal tract was Maxillary sinus. In this study, we attempted to determine the etiological diagnosis of sinonasal fungal infections and the Histopathological examination can render efficient identification of infectious fungal organisms and remains the only feasible and rapid means to identify fungal organisms for starting appropriate therapy for patients.

Keywords: fungal infections, sinonasal tract, histopathological diagnosis.

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INTRODUCTION

Fungal organisms are ubiquitous and common location for these organisms to enter the body is sinonasal cavity. There is 20,000 to 1.5 billion different fungal species and only a few can cause human disease. The two main forms of fungus are yeasts and molds. Yeasts forms pseudo hyphae and molds grow by branching true hyphae. Another important component of fungal organism is the spore, by which fungal organisms gain access on to the sinonasal tract [3]. Fungal sinus disease can be classified in to two categories – non-invasive and invasive. Non-invasive includes saprophytic fungal infestation, sinus fungal ball and allergic fungal sinusitis. Invasive disease includes acute fulminant invasive fungal sinusitis, chronic invasive fungal sinusitis, and granulomatous invasive fungal sinusitis [3].

Most species of fungal organisms which are pathogenic to human beings cause opportunistic infections and only dermatophytes are transmissible from person to person. The incidence of fungal infections and death due to fungi has been grossly undervalued and furthermore, the fungal species capable of producing disease in immunocompromised persons has been on the rapid rise [1].

In this modern era, therapy with protracted and extensive usage of broad spectrum antibiotics, Cancer chemotherapeutic agents, Immunosuppressive drugs, Irradiation, and use of radiological screening procedures, Organ transplantations, and Acquired immunodeficiency have led to rise in the incidence of overall fungal infections[2].

In our study, the fungal infections in the sinonasal tract clinically presented with nasal polyps, nasal block, nasal discharge, headache, proptosis and mass in the paranasal sinus mimicking benign or malignant neoplasms of the nose and paranasal sinuses. The agricultural economy in our area also accounts for the high prevalence of the fungal infections in the sinonasal tract. Among the fungal infections of nose and paranasal sinuses, Aspergillosis and mucormycosis tops the list in terms of occurrence.

Despite the consideration of the fact that microbiological examination with culture is a gold standard method for the diagnosis of fungal infection, it is time consuming [2]. The identification of some fungal infections by using microbiological examination alone will be challenging, because some fungi cannot be cultured and it will be misleading by contamination with other fungi [2]. In addition, lack of specificity in Serological reactions, uncommon detectability of certain fungi in body fluids and exudates owing to tight adherence to tissues, Histopathological examination emerged as one of the chief diagnostic tools in mycology, in view of rapid and presumptive identification of fungal infection and unprecedented diagnosis of fungal infections in tissues sent to identify the cause of chronic inflammation and to exclude malignancy [4, 5]. Moreover, Histopathological examination helps to distinguish between contamination, colonization and true infection of the organisms with the evidence of tissue invasion and inflammatory reaction surrounding the fungal elements [7]. Although, due to scanty organisms, morphological mimicking, and observer inexperience, histopathological tool may not identify fungal infections in all the instances, it aids in etiologic diagnosis in considerable number of cases, provided tissue adequacy has been maintained in all cases [6]. The aim of this study is to detect the type of fungal infections and their distribution according to age, sex, in histopathological specimens from sinonasal tract received in the Department of Pathology, Karpaga Vinayaga Medical College, Chengalpattu, Tamil Nadu, India. The histomorphology of various fungal organisms has been highlighted in our study in order to diagnose the fungal infections in histopathologic specimens in a more specific and accurate manner.

MATERIALS AND METHODS

This was a retrospective study carried out in the Department Of Pathology for a period of 3 years from February 2016 to February 2019. All the histopathological specimens from sinonasal tract which were diagnosed to have fungal infections during this study period were included in this study. Both clinically suspected cases and incidentally detected fungal infections of the nose and paranasal sinuses were included in this study. Specimens obtained from autopsy cases, specimens with other infections (bacterial, viral & parasitic) in other sites were excluded. The sections were stained with routine haematoxylin and eosin stain [H&E] and special stains such as Periodic Acid Schiff (PAS) and Gomori's methenamine silver (GMS) were performed and reviewed in specific cases. All medical records of the patients diagnosed histopathologically with fungal sinonasal disease were retrieved and clinical details including age, sex, predisposing conditions, symptoms and signs were obtained. Haematological, radiological and immunological investigation reports if any were also collected.

RESULTS

During this study period, Out of 11,301 total histopathological specimens, 2800 specimens were received from the site of nose and paranasal sinus from various departments including ENT and oral maxillofacial surgery etc., which constituted 24.77%. Out of those, 40 cases were found to have fungal infections, accounting for 0.35% of total histopathological specimens and 1.43% of sinonasal tract specimens. All these 40 cases were evaluated retrospectively for the following parameters – Age, Sex, Clinical symptoms and signs along with detailed histopathological examination (both H & E and special stains in specific cases). Out of 40 cases, 77.5% were males, 22.5% were females. The cases showed wide range of age incidence between 11 and 80 years. So it was noted in this study that there is no age predilection for the occurrence of fungal infections in the sinonasal tract. [Table 1, Chart 1].

Most of the patients, in our study presented with combined clinical symptoms including maxillary pain (32.5%) followed by other sinonasal tract symptoms such as nasal polyps, nasal obstruction, nasal discharge, postnasal discharge, frequent sneezing, reduced sense of smell (hyposmia) or complete loss of smell (anosmia), and nasal bleeding along with ocular symptoms, headache and mass in the paranasal sinus(12.5%) [Table 2, Chart 2].

The most common type of fungal infection was aspergillosis (14) followed by mucormycosis (11), others were rhinosporidiosis (6), phaeohypomycosis (2), candidiasis (2) and pigmented fungosis (3). In two cases, particular etiologic diagnosis could not be made and labelled as fungal granuloma based on noncaseating granuloma formation, tissue reaction, and vaguely made out fungal elements [Table 3, Chart 3]. The most common site of infection in the sinonasal tract was maxillary sinus (18 cases) followed by nasal cavity (11 cases), frontal sinus (4 cases), ethmoidal sinus (6 cases) and sphenoidal sinus (1 case) [Table 3].

Aspergillosis was the most common type of fungal infection in maxillary sinus (11 cases) followed by mucormycosis (5) and also one case each of phaeohypomycosis and pigmented fungosis was noted. Most of the cases of Aspergillosis presented with maxillary sinusitis (9) followed by polyp in paranasal sinuses (4) and nasal cavity (1) [Table 5]. In nasal cavity, six cases of Rhinosporidiosis, three cases of mucormycosis along with one case each of candidiasis and fungal granuloma were seen. Two cases of candidiasis were seen, in which one case seen in ethmoidal sinus was associated with squamous cell carcinoma. Two cases of phaeohypomycosis were noted, in which one case was suspected clinically as neoplastic lesion of the sphenoidal sinus and the patient was an agricultural worker. It was the only fungal

disease seen in sphenoidal sinus in our study [Table 3, Chart 3].

We marked three cases of fungal infections as pigmented fungosis which could not be differentiated between chromoblastomycosis and phaeohypomycosis with detailed histopathological examination. Out of those three cases, two were seen in frontal sinus and one case was seen in maxillary sinus [Table 3].

In our study, the predominant morphological tissue response to fungal infection in nose and paranasal sinus was marked chronic inflammatory infiltrate which is seen in 60% of cases. Other reactions were necrosis (20%), granulomatous inflammation (12.5%) and calcification (7.5%) [Table 4].

Table-1: Age and sex-wise distribution of fungal infections of the sinonasal tract

Age (years)	Male	Female	Total
11-20	1	0	1
21-30	2	1	3
31-40	3	2	5
41-50	10	4	14
51-60	6	1	7
61-70	8	1	9
71-80	1	0	1
Total	31	9	40

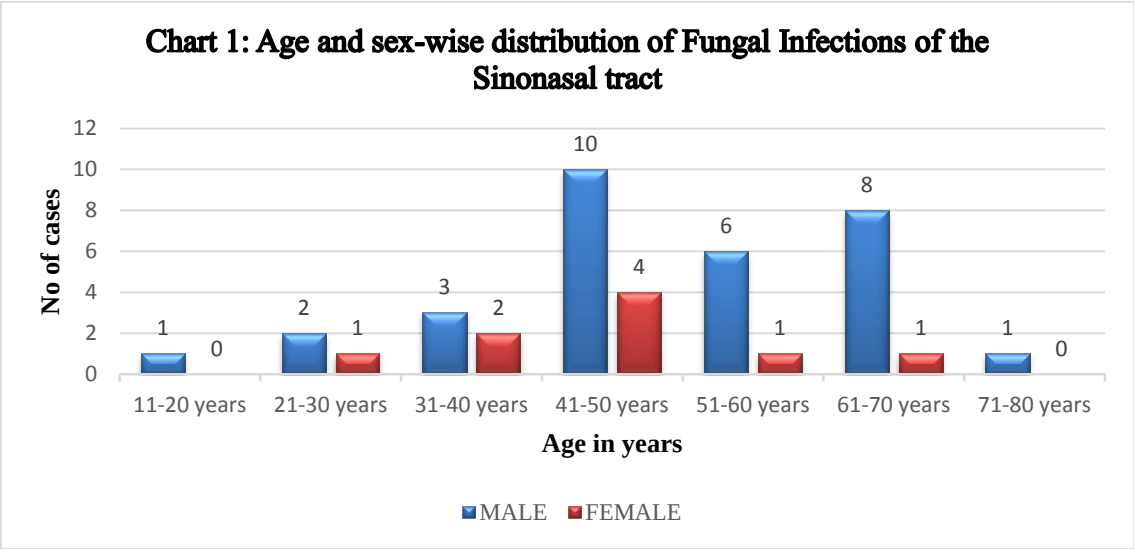

Table-2: Clinical symptoms [Total cases = 40]

Symptoms	Number of patients	Percentage (%)
1. Nasal • Nasal polyps • Nasal obstruction • Nasal discharge • Post nasal Discharge	10	25%
2. Headache	8	20%
3. Ocular symptoms	6	15%
4. Pain in the Maxillary area	13	32.5%
5. Mass in the paranasal sinus	5	12.5%

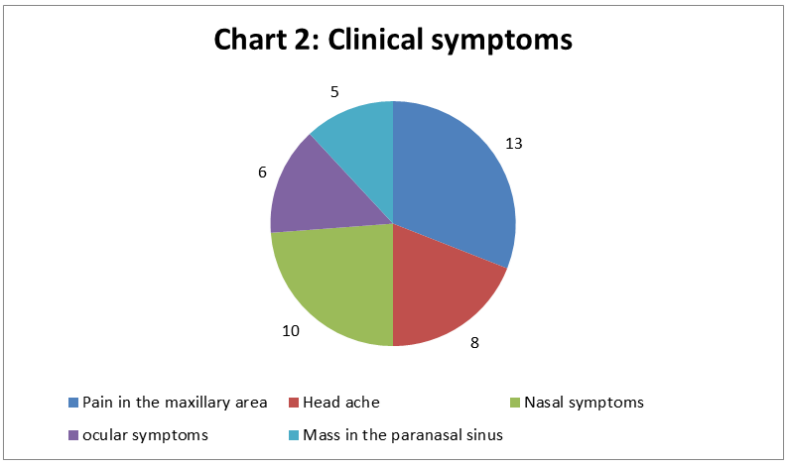

Table-3: Site of Distribution of Morphological subtypes of Sinonasal Fungal infections

	Nasal cavity	Frontal sinus	Ethmoidal sinus	Maxillary sinus	Sphenoidal sinus	Total
Rhinosporidiosis	6	-	-	-	-	6
Aspergillosis	-	1	2	11	-	14
Mucormycosis	3	1	2	5	-	11
Candidiasis	1	-	1	-	-	2
Phaeohypomycosis	-	-	-	1	1	2
Pigmented fungosis	-	2	-	1	-	3
Fungal granuloma	1	-	1	-	-	2
Total	11	4	6	18	1	40

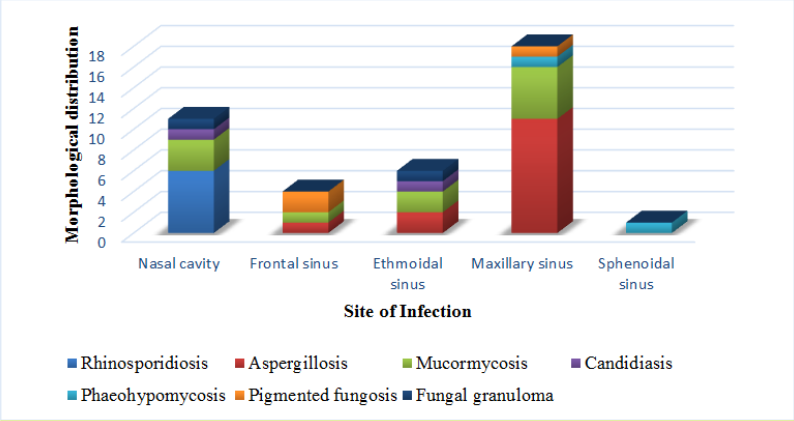

Chart-3: Site of Distribution of Fungal infections in the Sinonasal tract

Table-4: Host response to Mycosis

	Frequency	Percentage (%)
Necrosis	8	20
Granuloma	5	12.5
Marked Inflammation	24	60
Calcification	3	7.5
Total	40	100

Table-5: Clinical Diagnosis of Aspergillosis in the Sinonasal tract

	No of cases	Percentage (%)
Nasal Polyp	1	7.1
Maxillary sinusitis	9	64.3
Polyp in the Maxillary sinus	2	14.3
Ethmoidal Polyp	2	14.3
Total cases of Aspergillosis	14	100

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Table-6: Comparison with other studies

	Present study	Dufour *et al*. [14]	Muniyappa Usha *et al*. [2]	Sridevi *et al*. [8]
Sex	M>F	F>M	M>F	M>F
Age	11-80 yrs	14-87 yrs	10-70 yrs	10-80 yrs
Most Common fungal organism identified by morphology	Aspergillosis	Aspergillosis	Mucormycosis	Phaeohypomycosis
Common site	Maxillary sinus	Maxillary sinus	Maxillary sinus	Foot

DISCUSSION

Histopathological examination aids in the diagnosis of infectious fungal organisms and remains an important method of identifying certain pathogens in all the sites including the sinonasal tract. Though culture remains the standard method for definite diagnosis, by microbiological examination, we cannot differentiate contamination of fungi from colonizing pathogenic fungus and some fungi cannot be cultured [8]. Guarner, Brandt and Ramasundar *et al*. have identified the difficulties in differentiating colonization and contamination of fungi [9, 1].

In our study, out of 40 cases of fungal infections in the sinonasal tract, Aspergillosis stands the first. *Aspergillus* spp. are ubiquitous in the environment and *Aspergillus fumigatus* is the species most frequently associated with human disease, but other species, including *A. niger* can cause disease in immunosuppressed hosts. Aspergillosis can present as allergic bronchopulmonary aspergillosis (ABPA), chronic pulmonary aspergillosis/aspergilloma, and invasive or systemic aspergillosis. Tissue invasive and angio-invasive aspergillosis is found to be lethal, especially in immunocompromised hosts [10]. In our study, we had 11 cases of aspergillosis in the maxillary sinus (antrum), two cases in the ethmoidal sinus and one case in the frontal sinus, which was identified by thin walled (3 to 12 µm), septate, acute-angle (45°) and dichotomous branching hyphae (Fig.2). Out of 14 cases, 9 cases presented clinically as allergic fungal maxillary sinusitis which showed Allergic mucous with eosinophils, mucosa with suppurative or granulomatous inflammation, vasculitis and fibrosis. Other cases showed features of invasive disease in the form of angioinvasion by hyphae with consequent necrosis and haemorrhage of surrounding tissue. Two cases showed features of fungal ball (Fig 1) with abundant hyphae surrounded by granulation tissue and necrosis (Fig 3). Vesicles with conidia and fruiting body can also be observed in three cases of maxillary sinusitis (Fig 2).

The next common fungal infection in the sinonasal tract in our study was Mucormycosis (11 cases). The three most common clinical manifestations of Mucormycosis are rhinocerebral, pulmonary, and cutaneous infections [9]. Inhaled spores cause disease in the upper and lower respiratory tracts of immunocompromised persons [9]. Rhinocerebral mucormycosis is an invasive fungal infection that is initiated in the paranasal sinuses and frequently progresses to orbit and brain [11]. Diabetes is a most frequent and common risk factor for sinusitis, because it causes dysfunction of macrophages however, it also includes any immunocompromised state and trauma [9,11]. They were diagnosed morphologically in our study by irregular broad pauci-septate hyphae branching at right angles [8]. The hyphae are often folded or coiled [9]. In lesions of maxillary sinus (5 cases) and nasal cavity (3 cases) in our study, thick-walled spherical structures of chlamidoconidia were noted at the hyphal ends due to exposure to air [8,9]. (Fig 4).

We noted six cases of rhinosporidiosis in the nasal cavity. Guarner and Brandt *et al*. stated that diagnosis of rhinosporidiosis can be done only using histopathological examination. *R. seeberi* presents as large (50- to 100-mm) round structures that can be seen with the naked eye as yellowish pinhead-sized spots in the polyp [9]. Microscopically, it has a densely eosinophilic wall that either encloses smaller round structures and mucosa shows hyperplastic and metaplastic features, as in our case squamous metaplasia is seen (Fig 8). Granulomatous host response was seen in 3 out of 6 cases.

We noted 2 cases of phaeohypomycosis, one case in sphenoidal sinus and the other in maxillary sinus. Phaeohypomycosis comprises a heterogeneous group of subcutaneous and systemic infections caused by a wide variety of dematiaceous (naturally pigmented) opportunistic fungi [12] and are identified by the presence of pigmented yeast- like and hyphal forms [12]. These infections are life-threatening, and occur in various immunocompromised patients [8]. We identified the fungal elements as yeast-like structures and septate pigmented hyphae throughout the lesion (Fig 7). Clinically it presented as maxillary pain and mass lesion in the sphenoidal sinus which was suspicious of malignancy and the mass was grossly pigmented (Fig 6). With histopathological examination only, it could be detected as fungal infection in these two clinically unsuspected cases.

We had 3 cases of pigmented fungosis, 2 cases of candidiasis and 2 cases of fungal granuloma in our study. All the cases (2) of candidiasis were middle aged immunocompromised females with one case each in nasal cavity and ethmoidal sinus (associated with

squamous cell carcinoma). The three cases of pigmented fungosis in our study had darkly-pigmented hyphae and spores. They cause primarily two groups of infections: chromomycosis and phaeohypomycosis. The brown pigment in the fungi is a melanin, which can be precisely demonstrated in tissue sections by melanin stains [13] but they lack sclerotic bodies and muriform cells, so that they are categorised as pigmented fungosis. Gomez and Nosanchuk et al has referred melanin as "fungal Armor [13]". In 2 cases, the clinical presentation and the host tissue response (non-caseating granuloma) were highly suspicious of fungal infection with microbiological evidence of fungal growth, but only vague fungal elements were demonstrable in the tissue sent for histopathological examination which explains the importance of tissue adequacy for detailed histopathological examination and morphological identification of fungal elements.

The comparison between our study with other morphological studies of fungal diseases including other sites, showed that Aspergillosis was the most common fungal organism in the sinonasal tract in our study, corresponding with Dufour *et al.*[14] whereas in Muniyappa Usha *et al.* [2] and in Sridevi *et al.* [8] it was Mucormycosis and Phaeohypomycosis respectively, which was found to be common [Table 6].

Likewise in our study, Maxillary sinus was the commonest site of sinonasal fungal infection, which coincides with Muniyappa Usha *et al*. [2] and Dufour *et al*.[14] whereas in Sridevi *et al* which includes other sites also, foot was found to be the commonest site.

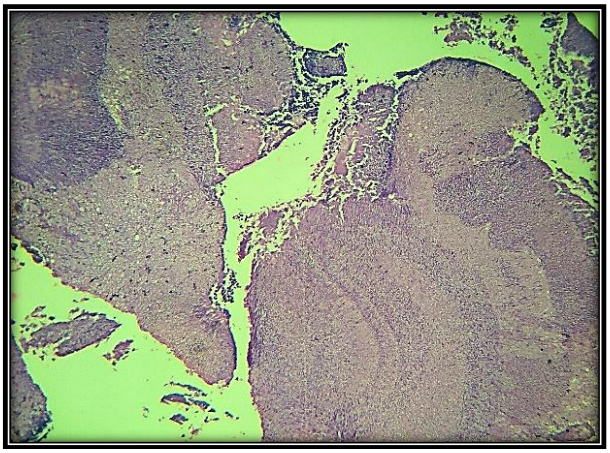

Fig-1: Low power view showing fungal ball of Aspergillosis with necrotic areas (H&E)

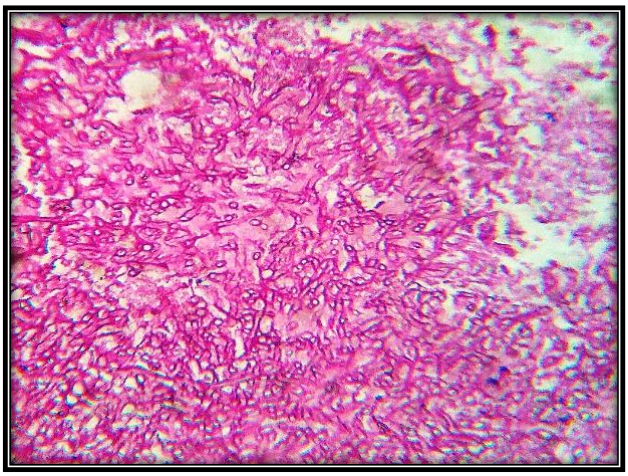

Fig-2: High power view showing thin acute angle branching fungal hyphae of Aspergillosis forming fruiting body (H&E)

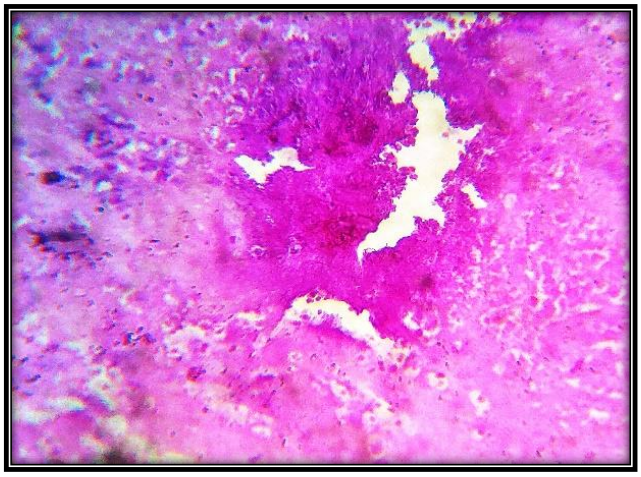

Fig-3: Low power view showing host tissue response in the form of necrosis admixed with few fungal elements

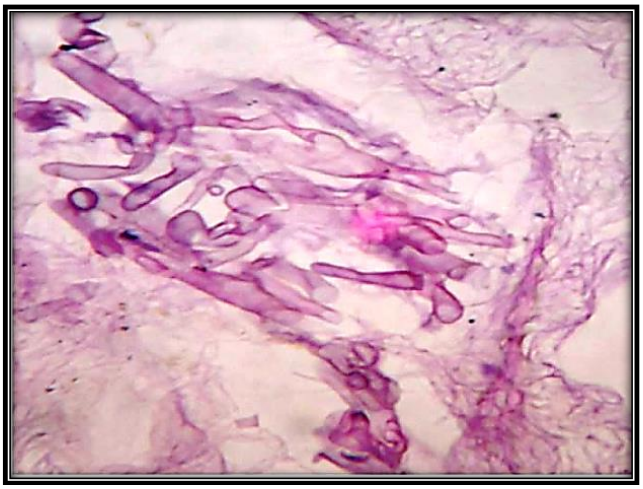

Fig-4: High power view showing broad aseptate hyphae of mucormycosis (H&E)

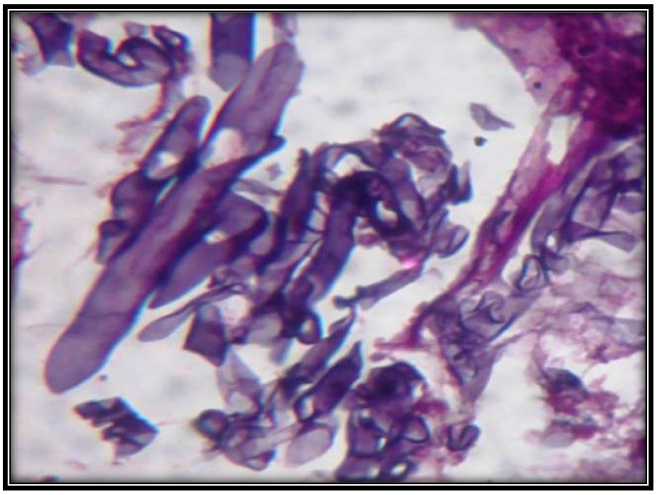

Fig-5: High power view showing fungal hyphae of mucormycosis stained with special Stain (PAS)

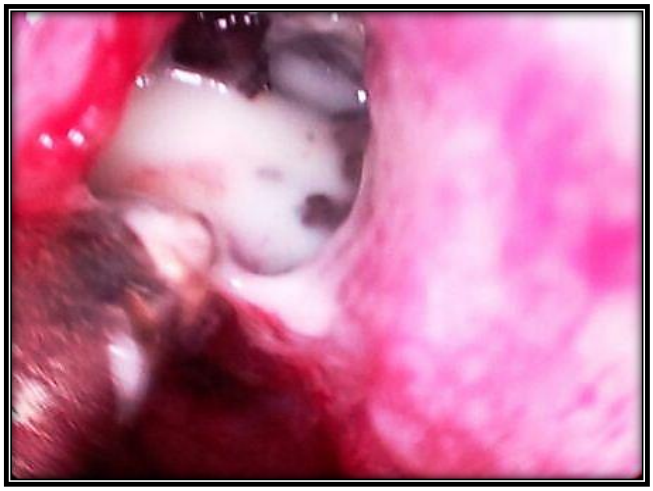

Fig-6: Endoscopic picture showing Mass in the sphenoidal sinus which is focally pigmented

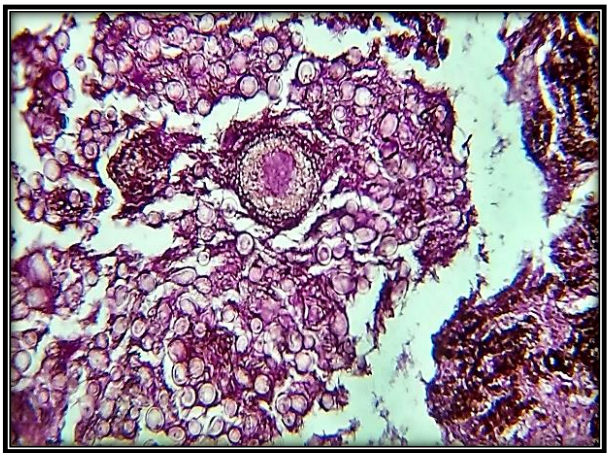

Fig-7: High power view showing pigmented hyphae and yeast forms of phaeohypomycosis (H&E)

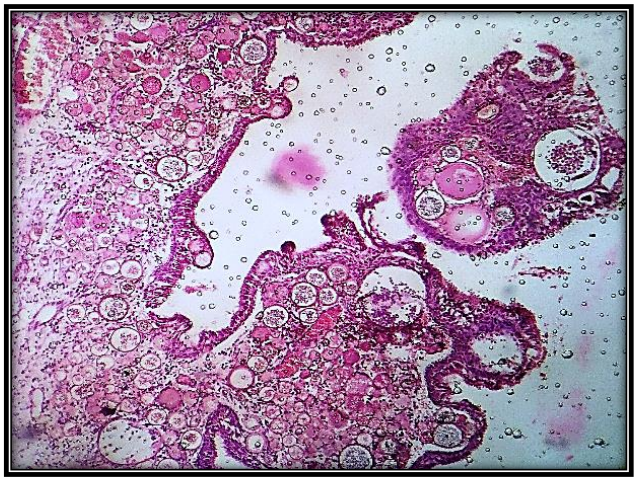

Fig-8: Low power view showing respiratory mucosa with focal squamous metaplasia and sporangium with spores of Rhinosporidiosis (H&E)

CONCLUSION

In our study we attempted to determine the etiological diagnosis of sinonasal fungal infections with special highlight to microscopic morphology in the histopathological specimens received in our Pathology Department. Though there were many histomorphological studies of fungal infections involving all sites, considering the fact that the most common site of entry of fungus is the sinonasal tract, we made an effort towards highlighting the histomorphological diagnosis of fungal infections in the nose and paranasal sinus. Due to the fact that culture makes slight delay in diagnosis of fungal infections, we conclude that the histopathological examination,

together with the special stain study can remain as stable and rapid mode of reliably diagnosing pathogenic fungal organisms by substantiating host tissue reaction along with fungal elements. Hence, Histomorphological diagnosis of sinonasal fungal infections prompts the clinician to initiate precise antifungal therapy and thus offers timely management of patients even in clinically unsuspected cases.

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