ORIGINAL ARTICLE

Mucormycosis During Second Wave of COVID-19 in India: Exploratory Analysis from Tertiary Care Centre of Uttar Pradesh

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Abstract

Background: In April and May 2021, India faced massive second wave of COVID-19 pandemic and then became the hotspots of mucormycosis across globe. Hence, we planned the first analysis of mucormycosis in Uttar Pradesh. **Aim and Objectives:** coThe objectives were to explore the epidemiology, vaccination status, clinical features, microbiological findings, treatment of mucormycosis and outcome. **Material and Methods**: This was an observational study of mucormycosis at tertiary care centre of Agra, Uttar Pradesh, India from 20 May 2021 to 15 July 2021. **Results**: 98 patients' data with mucormycosis was analyzed. Patients had median age of 55 years. COVID-19 infection was present in 69.4% of participants and diabetes mellitus was present as underlying co-morbid condition in more than 85% of patients. 91.8 % of cases were unvaccinated with steroid consumption in almost 60% of patients. R. arrhizus was among the most common agent while we found less commonly reported fungi like R.homothallicus, Apophysomyces, Cunninghamella. 41.8% of cases were successfully treated and 16.3% of cases expired. **Conclusion**: Diabetes mellitus was labeled as major predisposing factor and most patients were unvaccinated. Awareness about fungal infections, rigorous monitoring of chronic diseases, judicious use of drugs, early diagnosis and prompt treatment is decisive for better outcome.

Keywords

Mucormycosis; COVID- 19; Corticosteroids; Diabetes; India; Rhizopus

Introduction

In April and May 2021, Indians were gripped by massive (disastrous) second wave with the highest number of cases about 4 lakhs on May 7, 2021(1). India became the hotspots of coronavirus disease-associated mucormycosis (CAM) during second wave which was reported sporadically during first wave of COVID-19 (2). The Union health minister, informed Parliament of India on 20th July 2021 that a total of 45,432 cases of mucormycosis have been reported till 15th July 2021 of which 84.4% had Covid-19 infection (3). Mucormycosis, a serious and life-threatening angioinvasive fungal infection is caused by molds called mucormycetes, which live throughout the environment. Mucormycosis mainly targets immunocompromised hosts with uncontrolled diabetes in our part of world and patients with hematological malignancy, on chemotherapy, transplant recipients in west.

The rhino- orbital -cerebral mucormycosis (ROCM) is the most often presentation with nearly 50% mortality followed by pulmonary, cutaneous, gastrointestinal, and disseminated infections. (4,5,6,7). Emerging fungal infections is a growing concern worldwide, more so in India due to temperature adaptation, under- diagnosis, millions of diabetics and poor awareness (5,8,9). Globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million populations, while it is nearly 80 times higher

(0.14 per 1000) in India (10). Pandemic brought mucormycosis on horizon in India with share of 80% CAM across globe (10). Research on CAM during second wave underlines uncontrolled diabetes, widespread use of corticosteroids, long- term stays in the intensive care unit as factors for this surge of mucormycosis (6,7,10,11). Hence, we planned to do the first analysis of mucormycois in most populous state of India, Uttar Pradesh.

Aims & Objectives

1. The sociodemographic profile of patients with mucormycosis
2. COVID-19 status, risk factors, vaccination status of patients with mucormycosis
3. Clinical staging of disease, microbiological characteristics of circulating fungi and outcome of patients

Material & Methods

Study type, area and duration: We conducted an observational study at tertiary care centre of Agra district, Uttar Pradesh, India from 20 May 2021 to 15 July 2021.

Study Population: All consecutive patients of mucormycosis (clinically suspected) admitted in our tertiary centre during study duration were enrolled as study participants.

Data collection: We collected the following information about patients: (a) demographic details; (b) covid-19 status; (c) predisposing factors (diabetes mellitus, glucocorticoid therapy, transplant, malignancy, immunosuppression, and others, co-morbid conditions (ischemic heart disease, chronic kidney disease, chronic liver disease, chronic respiratory illnesses, and others); (d) vaccination status; (e) clinical features, site of disease with clinical staging rhino-orbital with or without cranial extension, cutaneous, renal, pulmonary, gastrointestinal and disseminated); (f) microbiological and histopathological features and species of fungi isolated ; (g) details of treatment given (antifungal agent, dose and duration of antifungal agent, nature of surgical treatment); and (h) Outcome of disease. Clinical staging was done as follows; stage 1(involvement of nasal mucosa), stage 2 (involvement of paranasal sinuses), stage 3 (involvement of orbit) and stage 4 (involvement of CNS) as per proposed guidelines of ROCM (7).

Working definition: The diagnosis of mucormycosis was made based on following case definitions; *Proven* mucormycosis was defined as histopathologic, cytopathologic or direct microscopic examination showing fungal hyphae in biopsy specimen with associated tissue damage, or a positive culture result. *Probable* mucormycosis was concluded as the presence of combined host factors and clinical criterion with mycological evidence and if only the criteria for a host factor and a clinical criterion were met but mycological criteria were absent, *possible* mucormycosis was diagnosed (6). Classification of COVID-19-associated rhino- orbital-cerebral mucormycosis (ROCM) as possible, probable, and proven (7) is shown in Table -1. The diagnosis of COVID-19 in patients admitted was based on any one of following parameter; reverse transcription polymerase chain reaction (RT-PCR) test on nasopharyngeal or oropharyngeal swabs, rapid antigen test, or computed tomography (CT) chest scores in the absence of a positive RT-PCR test in a clinically symptomatic case (6,7).

Processing of sample*:* The processing of samples from individuals with clinically suspected mucormycosis was done to make diagnosis of mucormycosis. Tissue samples from nasal/sinus biopsies and biopsies from ulcers in oral cavity of patient were sent for microbiology and pathology examinations. Samples were subjected to conventional microscopy, culture and histopathological examination, as appropriate. Microscopy was performed using the KOH mount preparation method. The patient samples were also inoculated onto two sets of Sabouraud Dextrose Agar (SDA) with antibiotics at both 25^0C and 37^0 C temperatures and brain heart infusion broth. The positive cultures were identified by their macroscopic and microscopic characteristics.

Treatment details: For successful management and better outcome of mucormycosis patients, all those who presented with a high index of clinical suspicion, were started immediately on systemic antifungal (Inj Amphotericin) alongside other supportive treatment. Magnetic resonance imaging (MRI) of orbit, brain, and paranasal sinuses with or without computed tomography (CT) was performed for assessing extent of the disease. All those suspected were subjected to emergency endoscopies and debridements were done for all, who consented, within 24 hours of admission to hospital. Based upon the KOH mount report and HPE of specimen subjected, further course of treatment was outlined. In all, teams comprising of otorhinolaryngology, ophthalmology and neurosurgeons did '72 surgeries'. Systemic antifungals were continued in conjunction with otorhinolaryngology, infectious disease specialists and nephrologists, till resolution of initially indicative findings on imaging and reconstitution of host immune system. Relook endoscopies were done every week along with radiological assessment and if needed progressive debridements were done. All patients with orbital involvement were further subjected to transcutaneous retrobulbar Amphotericin B (TRAMB) injection with 1 ml of 3.5 mg/ml solution for 3 to 7 days as needed. A coordinated and timely effort from a multidisciplinary team comprising of ophthalmology, otorhinolaryngology, infectious diseases, neurosurgery, critical care, nephrology, microbiology, and pathology department is crucial for preferred outcomes.

Ethical approval and data analysis: The Institute Ethics Committee of college approved (SNMC/IEC/2021/35) the study protocol and a written informed consent was

obtained from all the study subjects The data was recorded in Microsoft Excel and analyzed using statistical software, Microsoft Excel (Version 16.49). The results are presented accordingly in form of descriptive statistics. (8-11)

Results

A total of 98 participants' data was analyzed in this mucormycosis analysis. Patients in our study had median age of 55 years with range from 10 days neonate to 88 years. 63.3% of patients with mucormycosis were males and 37.8% were females. About 42% of study participants were from rural background. COVID-19 infection was present in 69.4% of participants, thus CAM (coronavirus associated mucormycosis). Predisposing factors for mucormycosis were identified in present study. Diabetes mellitus was present as underlying co-morbid condition in more than 85% of patients, newly onset diabetes was found in about 10% of cases and sugar levels ranged (at time of presentation) from 112 - 494 mg/dl with median value of 212 mg/dl. Other diseases present were hypertension (19.4%), cardiovascular disease (8%), chronic kidney disease (1.02%) and one case (1.02%) of renal cell carcinoma (after 4 years of nephrectomy). (Table-2)

Regarding vaccination with COVID-19 vaccine, only two cases (2.04%) were found to be fully vaccinated with two doses, six cases have received only one dose (6.12%), thus 91.8 % of cases were unvaccinated. Steroid consumption was present in 59 (60%) patients while 22 (22.5%) gave history that they do not know. Remdesivir was used by 10.2% of cases; half of cases (50.0%) used ayurvedic drugs and 37.6% had history of LMWH (low molecular weight heparin) usage. Forty-two (42.9%) cases gave history of hospital stay for COVID illness. Most common signs and symptoms at time of presentation were headache (86.7%), facial /periorbital/cheek swelling (68.4%), pain and redness in eye (42.9%), oral ulcers (38.8), nasal congestion/discharge (33.7%), fever (21.4%), respiratory difficulty, (14.3) cranial nerve palsy [3,4,6] (13.3%), altered sensorium (10.2%) . (Table-2)

Most cases (except two) detected with ROCM types (rhino-orbito-cerebral mucormycosis) mucormycosis. Clinical and radiological involvement of the PNS, orbit, and CNS are also shown in Table 1. 3.12 % of cases were in stage 1(involvement of nasal mucosa), stage 2 (involvement of paranasal sinuses) was reported in maximum number of cases (58.3%), stage 3 (involvement of orbit) was seen in 24% of cases while stage 4 (involvement of CNS) was found in 14.6% of cases. (Table-2) One case each of cutaneous and pulmonary type was diagnosed. Case of *cutaneous* mucormycosis presented to our centre; a 10 days female neonate from rural Agra, no history of COVID-19 infection, she was a diagnosed case of patent ductus arteriosus (PDA), portal hypertension (PHTN) and preterm delivery, she stayed in hospital and oxygen was given during that duration (Figure 1 and Figure 2) Another, one case of *pulmonary* fungal infection; a 43 year female with symptoms of fever, cough, respiratory difficulty from urban Agra was reported with hyperglycemia, steroid &oxygen use, history of hospital stay.

Microbiological findings of mucormycosis were reported in 82.71% of cases. R. arrhizus as most common fungi (61.4) followed by R.microsporus (6.5%) and R.homothallicus (0.03%). Other species isolated were Mucor (0.06%), two different fungi (Aspergillus and Mucor) were found together in two cases (0.06%) , Apophysomyces 0.06%), Rhizomucour (0.03%), Cunninghamella (0.03%) and *L*ichtheimia (0.03%) (Figure 3, Figure 4 and Figure 5). Rhizopus arrhizus was identified in cutaneous mucormycosis case. Aspergillus was isolated in case with pulmonary form. In terms of outcome of patients with mucormycosis after treatment, 41.8% of cases were successfully treated, 31.6% are under treatment, 10.2% were left to follow-up and 16.3% of cases expired. (Table-2)

Discussion

As of 20th July 2021, globally there have been more than 190 million cases and 4 million deaths due to COVID-19 pandemic(12). During mounting second wave in India, we were agonized with dual problem of covid-19 cases and fungal infection, mucormycosis. We reported first detailed analysis from Uttar Pradesh on mucormycosis. In context of demographic profile, we observed *mucormycosis youngest patient from India*, a female neonate of 10 days when she was admitted in our hospital. Median age of patients with mucormycosis in our study was 55 years (range 10 days neonate to 88 years). Likewise, a global review on CAM found 55 years as median age (range 10–86 years) (13). While two national multicentric studies found the mean age in CAM as 51.9 (range, 12–88) years and 53.4 years (7,14) ; two case series of 6 and 10 patients reported mean age as 60.5 and 55.8 years respectively (6,15). Press brief on mucormycosis by MoHFW on 28th June 2021 reported that majority of patients (42%) with mucormycosis were in age group 45-60 years (16).

There is male preponderance with mucormycosis infection as observed in studies during COVID and pre-COVID times. Two pan- India study and a metaanlysis (till May 2021) done during second wave observed that 71-75% were males who had CAM (7,10,14). Our analysis showed slightly less proportion of males (62.2%) infected with mucormycosis. *Ours is the only study which reported about area of residence among studies done so far*, with more than 40% participants from rural area of Uttar Pradesh. Nearly 69.4% participants had covid-19 infection as per case definition, but this number could be higher as we didn't include diagnosis of COVID-19 on basis of clinical symptoms. As mucormycosis graph mirrors with surge and

fall of second wave in India, there are high chances that more of these study participants were covid-19 positive. Secondly, about 42% of study participants were from rural area and they are less likely to get covid-19 test done for various reasons.

In beginning of pandemic, secondary fungal infections accounted for <1% to 6% in COVID-19 patients (14,17). A multicentric study (Sept. to Dec 2020) showed that of total mucormycosis cases 65.2% had COVID-19 and stressed a 2.1-fold increase in CAM with marginal difference in non-COVID-19 mucormycosis cases during same duration in 2019(18). Press brief by MOHFW on emerging cases of mucormycosis underlined that 86% of cases had Covid-19 infection(16). A systematic review (May 2021) reported sharp rise in CAM more in India (10). Why huge upsurge of CAM during second wave in India? This question is still unanswered with certainty. However, CAM has occurred in milieu of huge diabetic population; misuse of steroids; specific pathophysiological changes linked with mucormycosis in SARS-CoV 2 viral infection (alteration in T- cell population, dysregulation of ACE-2 expression in the pancreatic beta cells, insulin resistance) (19,20); heightened prevalence and virulence of Mucorales strains and increased risk inflicted by variants predominating in India (ie, the Delta variant) (21)

Diabetes mellitus was reported to be most common predisposing factor in present analysis. Comparably, studies and systematic reviews found diabetes as undisputed risk factor in mucormycosis during and before pandemic (4-8,10,16,19,22). Report by MoHFW, GOI cites that diabetes history was present in 64.11% of cases of Mucormycosis in 2021(16). With a rich milieu of 100 millions diabetics, uncontrolled diabetic population in India, there will be a serious risk of rising fungal infections to proportion of epidemics. Diabetes mellitus is a major risk factor in mucormycosis in Mexico (72%), Iran (75%) and USA (52%), but not much in Europe (8,23). Though we didn't find any case with post transplant, haematological malignancies, post-pulmonary tuberculosis in our study. Nevertheless, these are found as potential risk factors in published literature on mucormycosis; hence there is a strong association of co-morbidities and fungal-coinfection (5,8,9,21).

History of corticosteroid intake for the treatment of COVID-19 was present in 76.3 - 88% of cases in several studies (10, 24). We found steroid use in 60% of patients (22% said they do not know). Steroid use is a double-edged sword, labeled as effective drug in survival of COVID-19 patients (25), steroids consumption carry substantial risk of opportunistic fungal infection (10,26). This is coupled with diabetes, widespread use of steroids, self-medication, prescribing steroids even in mild COVID-19 cases (19,20). A large study from Mumbai (5428 hospitalized Covid-19 patients) during second wave reported not a single case ROCM; authors attributed this zero incidence due to low dose corticosteroid protocol and strict glycemic control (27). Immunomodulatory drugs such as tocilizumab, remdesivir could further increase the risk of secondary infections including fungal in COVID-19 patients (19,28). 10% had history of remdesivir use while no case of tocilizumab consumption in our study. Similarly, multicentric studies reported history of remdesivir usage (10%) and tocilizumab usage by fewer cases of mucormycosis (2.1- 2.7%) (5,7). We found that *91.8 % of cases were unvaccinated, none of studies described vaccination* in mucormycosis during pandemic.

As delay in seeking medical care, diagnosis and treatment for mucormycosis decreases chances of survival by many fold, awareness around red flag signs of mucormycosis is imperative among populations and clinicians. Patients presented with following most common complains at our centre; headache, facial /periorbital/cheek swelling,pain and redness in eye, nasal congestion/discharge, fever, oral ulcers. Similary, Sen *et al* (2021) described loss of vision, orbital/facial pain, periocular/facial edema, ptosis, and nasal discharge as most frequent presentations (7). *Not many studies have reported signs and symptoms.* The signs and symptoms of orbital mucormycosis are not different from those of mucormycosis in non-COVID-19 patients(6). COVID-19 patient hospitalized with moderate to severe infection or diabetics with COVID-19 or those receiving systemic corticosteroids should be screened for these signs. The 1950 Smith and Krichner criteria for the clinical diagnosis of mucormycosis are still considered to be gold standard and include(29) (black, necrotic turbinate's, blood-tinged nasal discharge and facial pain, soft peri-orbital or peri-nasal swelling with discoloration and induration, ptosis, proptosis of the eyeball and complete ophthalmoplegia and, multiple cranial nerve palsies unrelated to documented lesions).

Depending on the site of infection it is classified as rhinocerebral/ sino-orbital, pulmonary, cutaneous, gastrointestinal, and disseminated. All cases were of RCOM type except two, which were, classified as cutaneous and pulmonary each. Commonest organ involved with mucormycosis was nose and sinus (88.9%), then rhino-orbital (56.7%) and ROCM type (22.2%). ROCM mucormycosis is the commonest form followed by cutaneous, pulmonary, renal, gastrointestinal and disseminated infections.(7,10,25,30-32) Mucormycosis is third most common fungi reported after aspergillosis and candidiaisis(33). Spectrum of isolated mucorales isolated in our study ranged from*; Rhizopus arrhizus* as the most common agent causing mucormycosis also in research from done in India and globally (4,5,8,24). We found less commonly reported fungi like *R.homothallicus, Apophysomyces, Cunninghamella.* Cutaneous mucormycosis type has R. arrhizus as causative agent contrary to Apophysomyces species, which is found commonly in India (4,5).

For successful management and better outcomes of mucormycosis, with a high index of clinical suspicion, all

suspected mucormycosis started with treatment at our centre. In terms of outcome of patients with mucormycosis after treatment, 41.8% of cases were successfully treated, 31.6% are under treatment, 10.2% were lost to follow-up and 16.3% of cases expired. The sequential use of antifungal drugs at any site was associated with improved survival at 6 and 12 weeks, irrespective of anatomical site of mucormycosis. In low- and middle-income countries including India, mucormycosis is associated with high mortality (45 %-90%). For cases associated with COVID-19, the overall mortality has been estimated to be 14-53% (6,7,10). A delay of even 6 days in initiating treatment doubles the 30-day mortality from 35% to 66%. (6) That is one of the reasons it was declared an epidemic, to mount an urgent response.

Conclusion

We described series of 98 cases in present exploratory analysis of mucormysosis. Male of median age 55 years being more infected with mucormycosis; diabetes mellitus sweeping the ground as major predisposing factor and history of vaccination being absent in most patients. A combined surgical and medical management was associated with better outcomes. Some less commonly fungi were isolated which desires urgent introspection into growing fungal opportunistic infections. Awareness about fungal infections, rigorous monitoring of chronic diseases, judicious use of drugs, early diagnosis and prompt treatment is decisive for better survival. Further research into association with variants of COVID-19 virus, hospital related risk factors including ICU settings and regional factors are needed.

Recommendation

Fungal infections are important growing opportunistic infections in India. Awareness about fungal infections, rigorous monitoring of chronic diseases, judicious use of drugs, early diagnosis and prompt treatment is decisive for better survival. Further research into association with variants of COVID-19 virus, hospital related risk factors including ICU settings and regional factors are needed.

Limitation of the study

Our study is limited to only one centre and probably have a referral bias due to tertiary care setting

Relevance of the study

This is *first analysis from Uttar Pradesh* on mucormycosis during second wave of covid-19 pandemic. This research will provide a detailed insight into all domains of mucormycosis from epidemiology, CAM (COVID-19 associated mucormycosis), vaccination status of cases, clinical profile, micrbiological findings and outcome. This research from country will provide inputs about this deadly fungus, in this crucial phase of pandemic and about mucormycosis.

Authors Contribution

APS and MKB designed study and collection of data; GS – conceptualization of study analyzed data and manuscript preparation; VK and MK - collection of data, All authors contributed in editing manuscript.

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Tables

TABLE 1 CLASSIFICATION OF COVID-19-ASSOCIATED RHINO- ORBITAL-CEREBRAL MUCORMYCOSIS (ROCM) AS POSSIBLE, PROBABLE, AND PROVEN

Terminology	Definition
Possible ROCM	Typical symptoms and signs of ROCM Clinical setting of concurrent or recently treated COVID-19
Probable ROCM	Clinical features suggestive of ROCM Supportive diagnostic nasal endoscopy findings and/or Supportive radiological signs on contrast-enhanced magnetic resonance imaging or computed tomography scan
Proven ROCM	Clinico-radiological features suggestive of ROCM Microbiological confirmation on direct microscopy and/or Culture and/ or Histopathology with special stains and/or Molecular diagnostics

TABLE 2 BASELINE CHARACTERISTICS, PREDISPOSING FACTORS, CLINICAL PROFILE AND DIAGNOSES OF STUDY PARTICIPANTS WITH MUCORMYCOSIS (N = 98)

	Parameters	n (%)
Age (in years)	Median age	55
Gender	Females	37(37.8)
	Males	62(63.3)
Predisposing factors	Diabetes Mellitus	84(85.7)
	Newly onset Diabetes mellitus	10(10.2)
	Hypertension	19(19.4)
	Cardio vascular disease	8(8.1)
	Chronic Kidney Disease	1(1.02)
	Malignancy	1(1.02)
Signs and Symptoms at time of presentation*	Facial /Periorbital/Cheek swelling	67(68.4)
	Pain and Redness in eye	42(42.9)
	Headache	85(86.7)
	Nasal congestion/discharge	33(33.7)
	Fever	21(21.4)
	Oral Ulcers	38(38.8)
	Respiratory difficulty	14(14.3)

	Altered sensorium Cranial Nerve palsy (3,4,6)	10(10.2) 13(13.3)
Drugs usage	Steroids Remdesivir Tocilizumab Ayurvedic drugs LMWH (Low molecular weight heparin)	59(60) 10(10.2) 0(0.0) 49(50.0) 37(37.6)
Clinical staging of RCOM (n=96) #	Stage 1 Stage 2 Stage 3 Stage 4	3(3.12) 56(58.3) 23(24.0) 14(14.6)
Diagnosis @ (n=81)	Direct Microscopy (KOH mount) Culture positive	69(82.7) 31(38.3)

(Figures in parentheses indicate percentages) SEP ** Multiple responses # Two cases, each of cutaneous and Pulmonary were not included as staging is for RCOM. @ For cases which microbiological evidence was found*

Figures

FIGURE 1 RHINO-ORBITO-CEREBRAL MUCORMYCOSIS: A- RIGHT EYE PTOSIS, B- POST SURGERY AND TRAMB THERAPY, C- MRI SHOWING COMPLICATED INTRAORBITAL EXTRACONAL ABSCESS

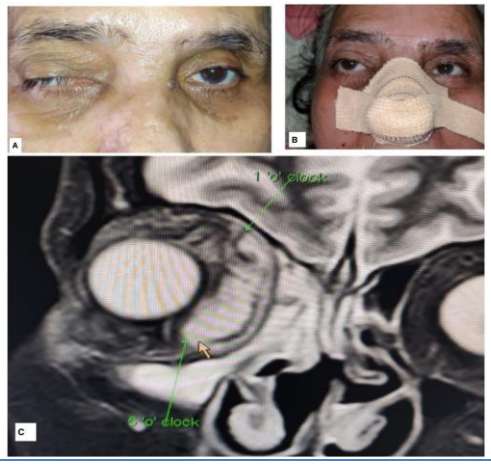

FIGURE 2 CUTANEOUS MUCORMYCOSIS: A- NECROTIC ULCER ON LEFT CHEEK AT PRESENTATION, B- AFTER 7 DAYS OF DEBRIDEMENT AND SYSTEMIC ANTIFUNGAL THERAPY, C- 7 DAYS AFTER PRIMARY WOUND CLOSURE,D- FUNGUS (RHIZOPUS ARRHIZUS) AS DEMONSTRATED ON KOH MOUNT

FIGURE 3 CUNNINGHAMELLA SPECIES ON LACTOPHENOL COTTON BLUE (LCB) MOUNT

FIGURE 4 RHIZOPUS HOMOTHALLICUS SPECIES ON LACTOPHENOL COTTON BLUE (LCB) MOUNT.

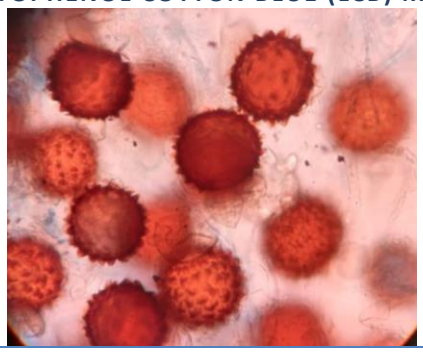

FIGURE 5 APOPHYSOMYCES SPECIES ON LACTOPHENOL COTTON BLUE (LCB) MOUNT