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A Review of Blastomycosis in Indian Subcontinent

Harish C Gugnani[1]*, Anuradha Sharma[2] and Neelam Sood[3]

[1]Dept. of Microbiology (Retired), Vallabhbhai Patel Chest Institute, University of Delhi, Delhi-110007, India; [2]Dept. of Microbiology, All India Institute of Medical Sciences, Bilaspur (HP), India; [3]Dept. of Lab Medicine Deen Dayal Upadhyaya Hospital, New Delhi-110058, India.

*Correspondence: harish.gugnani@gmail.com (Harish C Gugnani, Professor, Dept. of Microbiology (Retired), Vallabhbhai Patel Chest Institute, University of Delhi, Delhi-110007, India).

ABSTRACT

This study traces earliest cases of blastomycosis reported from India. Four authentic cases of blastomycosis from India including one each from Arunachal Pradesh, Himachal Pradesh, Kerala, and one each from Bangladesh and Nepal, and five misdiagnosed cases have been reported in India after 2013. The clinical and diagnostic features of all cases are reviewed. The authentic cases from India originate from widespread locations in the country. Incidence of blastomycosis in dogs is known to be eight to ten times higher than that in humans. There is only case of canine blastomycosis from India manifesting as fatal pulmonary infection in a Mongrel dog. It is suggested additional canine cases should be looked for in different parts of India to facilitate detection of endemic foci of *B. dermatitidis* for human and animal infections in the country. Mycological investigation of cases of pulmonary tuberculosis negative for culture and AFBs mear, and not responding to anti-tubercular therapy may reveal some cases of blastomycosis. A recently developed real-time PCR for identification of *B. dermatitidis* in culture and tissue may facilitate correct diagnosis of blastomycosis in suspected cases. Antigen testing in urine or serum is also recommended for diagnosing clinical infection and monitoring antifungal therapy in blastomycosis.

Keywords: Blastomycosis, Real-time PCR, Indian subcontinent, *B. dermatitidis*, Status, and Review.

INTRODUCTION:

Blastomycosis is a systemic mycosis caused by thermally dimorphic fungi, *Blastomyces dermatitidis* and *B. gilchristii*. Infection is acquired by inhalation of the organism, followed by its multiplication in the lungs and frequent hematogenous dissemination. Direct inoculation of the fungus is a rare means of infection (Sarcante and Woods, 2010; Benedict *et al*., 2012). The incubation period varies from 2 to 15 weeks, and the clinical spectrum ranges from asymptomatic to life-threatening infections involving acute respiratory distress syndrome or extra pulmonary dissemination (Sarcante and Woods, 2010) Most identified cases involve pulmonary infection that manifests similarly to other causes of pneumonia (Benedict *et al*., 2012; Hayle *et al*., 2020; Schwartz *et al*., 2018).

The clinical similarities between blastomycosis and other pulmonary infections often result in diagnostic delays and unnecessary empiric antimicrobial drug treatment for suspected bacterial pneumonia (Schwartz *et al*., 2018). The endemic areas for blastomycosis include states and provinces along Ohio, Mississippi, Missouri, and St. Lawrence River, Canada, Europe, Central America, and India (Sarcante and Woods, 2010; Thompson *et al*., 2017).

In reviews of autochthonous cases of blastomycosis from reported from Africa and India (Schwartz *et al*., 2021; Randhawa *et al*., 2013), it was found that 100 patients with this disease were reported from12 African countries, whereas only 10 were described from India. *Blastomyces gilchristii* is restricted to select Canadian provinces and northern US states, specifically, Alberta, Saskatchewan, British Columbia, Ontario, New York, Minnesota, and Wisconsin (Thompson *et al*., 2017). Schwartz *et al*. (2019) described a new species of Blastomyces, *Blastomyces helicus*, and an emerging pathogen for humans and animals in western Canada and United States. No case of *B. gilchristii* or *B. helicus* infection is known from Indian subcontinent.

METHODOLOGY:

A thorough search of the literature was made on blastomycosis cases reported in countries in the Indian subcontinent in PubMed, MEDLINE, Med Facts using sets of different keywords, viz. India, Bangladesh, Pakistan, Nepal, Bhutan, Sri Lanka, Blastomyces, systemic/deep mycosis, etc. Cross references in the relevant articles were used to download the papers and extract relevant information for incorporation in the review.

RESULTS:

Literature search revealed that the first report of *Blastomyces dermatitidis* infection from India was by Ganguli in 1925, described as a very common affliction prevalent in the rainy season, generally affecting t10-40% coolies working in the tea gardens of Duars situated at the foot of hills in east central Himalayas. From the lesions described as multiple warty ulcerated growths sometimes appearing granuloma to us and the detection of roundy east like cells scraping s of the lesions described, this report evidences a misdiagnosis of Blastomycosis as these are clinical and histological features of chromo blastomycosis. Again in1925, Panja described a case of generalized Blastomycosis with no dularsk in lesions and yeast-like cells in scrapings. The diagnosis of these two cases is dubious as pointed out in a review by Randhawa *et al*. (2013).

These authors have reviewed eleven cases of chromoblastomycosis including four authentic cases (including two autochthonous and two imported ones) and seven misdiagnosed ones reported in India up to 2013. The two autochthonous cases comprised one each from Uttar Pradesh and Madhya Pradesh. Our review has located three more authentically diagnosed indigenous cases in India including one each from Arunachal Pradesh (Kumar *et al*., 2014) Himachal Pradesh (Sharma *et al*., 2015) and Kerala (Kumar *et al*., 2019). One authentically diagnosed case each was reported from Bangladesh (Bhuiyan *et al*., 2015) and Nepal (Gandhi *et al*., 2015). Also, of five misdiagnosed cases published from India, one each was from Haryana (Rana *et al*., 2015) and Uttar Pradesh (Shekhar *et al*., 2016) two from Gujarat (Patel *et al*., 2014; Hongal & Geije, 2016) and one from Andhra Pradesh (Rao *et al*., 2013). The salient clinical features of autochthonous authentic cases of blastomycosis reported from India, Bangladesh and Nepal, and the misdiagnosed ones from India after 2013 are described in **Table 1**. The state-wise distribution of three Indian authentic indigenous cases of blastomycosis known so far after 2013 in **Fig. 1**.

Abbreviations

CNS-Central nervous system, CSF-Cerebrospinal fluid, h/o- History of, H & E-Haematoxiin and Eosin, PAS-Periodic Acid-Shiff, GMS-Groctt's methenamine silver, FNAC- Fine needle aspiration cytology, ATT-Antitubercular therapy

DISCUSSION:

The clinical and diagnostic features of the cases reported from India up to 1997 have been described earlier (Randhawa *et al*., 2013), Though the total number of authentic indigenous cases known form India so far is only six; their locations represent several parts of India, indicating that many more cases of Blastomycosis possibly exist in country but have not been diagnosed. Prolonged blastomycosis results inchronic cough, weightloss, and hemoptysis (Benedict *et al*., 2012). Pulmonary tuberculosis is quite common in the Indian subcontinent and is often treat dempirically. Mycological investigation of tuberculosis cases, negative for culture and AFBs mear, and not responding to anti-tubercular therapy may reveal some cases of blastomycosis. The areas of environmental distribution of *B. dermatitidis* in India remain undetermined *et al*. Isolation of *B. dermatitidi*a has been reported from the lungs of the bat, *Rhino-*

pomahardwickeihardwickei (Khan *et al*., 1982) and the liver of same bats pieces (Randhawa *et al*., 1985) in India. It is not known whether bats could be are a reservoir for human infections due to this fungus. In the USA, blastomycosis quite common in dog's residing in or visiting enzootic areas and the incidence of blastomycosis in dogs is eight to ten times higher than that in humans (Schwartz *et al*., 2018). Most dogs infected by inhaling spores of *B. dermatitidis* from soilor organic debris. Detection of Blastomycosis in dogs is a sentinel of possible occurrence of human cases of this disease (Benedict *et al*., 2012, Schwartz *et al*., 2018).

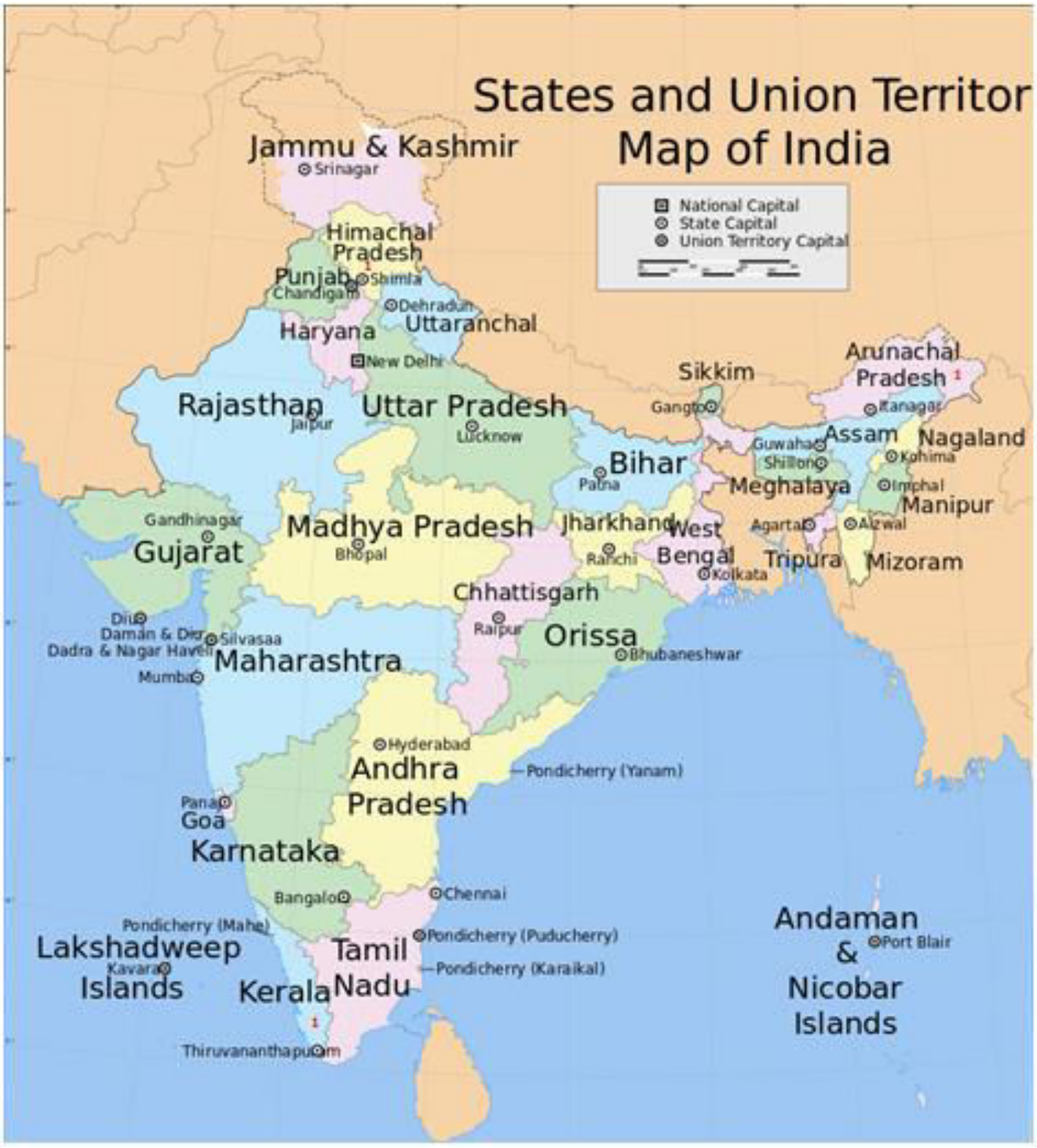

Fig. 1: The state-wise distribution of three Indian authentic indigenous cases of blastomycosis known so far after 2013.

Table 1: Salient clinical features of all the cases of blastomycosis reported after 2013 from the Indian sub-continent

Serial No Age/Sex	Symptoms	Basis of diagnosis	Therapy	Outcome	Reference/ Authenticity
Cases from India					
65/M Himachal Pradesh	Disseminated pulmonary infection with CNS and eye involvement	Demonstration of broad-based budding yeast cells characteristic of *B. dermatitidis* in CSF, sputum, and scrapings from the nose and soft palate lesion, *B.* Dermatitid is was also recovered in cultures.	Intravenous Amphotericn B. The patient developed side reactions of shaking chills and high fever	He developed disseminated intravascular coagulation and left the hospital against medical advice	Sharma *et al.* (2015)/ Authentic
53/M Arunachal Pradesh	Bilateral adrenal enlargement with mild cyanosis, clubbing, fatty hepatomegaly, mild splenomegaly, h/o smoking for 39 yrs. and diabetes for 5 yrs.	Demonstration of broad-based yeast cells in PAS and GMS-stained sections of adrenal biopsy, and recovery of *B. dermatiitidis* in culture of pus obtained by a repeat biopsy	Itraconazole 200 mg twice daily for three months	Monthly follow-up showed remarkable improvement with resolution of the lesion after three months as seen in ultrasonography of the abdomen	Kumar *et al.* (2016)/ Authentic
32/M Kerala	Multiple discharging sinuses on the anterior chest wall, h/o of travel to Chicago, USA, and ATT for 12 months	Demonstration of characteristic yeast forms in PAS and GMS-stained tissue sections	Itraconazole 200 mg twice daily for 12 months	The chest wall sinuses closed, and the sinus lines disappeared	Kumar *et al.* (2019)/ Authentic
40/M Haryana	Gross pathology of lung showed consolidation of parenchyma with numerous small. scattered nodules, Microsection showed focally haemorrhagic pneumonia	Demonstration of rounded to oval yeast cells with broad-based doubly contoured yeast cells with occasional hyphal forms	Fatal case	Not applicable	Rana *et al.* (2015)/ Not acceptable, as histology showed yeast cells with hyphal forms, which are not characteristic of *B. dermatitidis*.
12/M Uttar Pradesh	Multiple hyperkeratotic suppurating ulcers of varying size on the face, chest and limbs for 8 months. Ulcers were mobile and pus was draining from some of the ulcers	Clusters of large, variably sized, thick-walled, broad-based, multiple budding brown coloured refractile cells and hyphae like rows of budding cells seen in H & E and PAS-stained tissue sections	Started on oral itraconazole 5mg/kg/day. Intravenous (I.V) along with sefoperezone and sulbactam combination was started along with vancomycin 3mg/kg/day.	His skin lesions improved following which he was give three packed blood transfusions over a period of 7 days. The child became unconscious on 4th day and then started on I.V. amphotericin B 5mg/kg, Unfortunately the child died.	Shekhar *et al.* (2016)/ Not acceptable, since the lesions and the histopathology were characteristic of chromo-blastomycosis, rather than blastomycosis. It was a very poorly managed case.

37/M Gujarat	Multiple small maculopapular, firm nodules with sinuses on the middle third of the dorsal aspect of the knee, h/o renal transplant	Clusters of yeast cells and presence of IgG serum antibodies to *B. dermatitidis*. Cultures not successful	Initial treatment with fluconazole failed, switched to Itraconazole 400 mg daily. Duration not mentioned	The lesions healed	Patel *et al.* (2014)/ Not acceptable as examination of the histology image in the publication showed only one budding yeast cell and a pseu-dohypa.
35/M Gujarat	Multiple small Vegetations over the upper limbs, lower right leg, a few ulcers on right arm and crusted ulcers over the mammaryarea.	Diagnosed merely on appearance of the clinical lesions.	The lesions star-ted to heal. The patient was given cefaxine and advised to stop smoking & alcohol consumption.		Hongal andGeije(2016)/ Not acceptable, as clinical lesions are rather suggestive of chromoblasto-mycosis.
4/M Andhra Pradesh	Multiple hyperkeratotic, verrucose, suppurating plaques and nodules over the face, chest back and multiple umbilicated papules and nodules on extremities and a huge intraocular flesh-coloured mass in the left eye. FNAC of the cervical lymph nodes showed non-specific lymphadenitis.	Clinical lesions not suggestive. Illustrations indicating B. dermatitidis in tissue sections not provided.	.		Rao *et al.* (2014)/ Not accepted since clinical lesions are not suggestive of blastomycosis and no illustration of yeast cells *B. dermatitidis* was provided. There was also poorly managed case.
Cases from Bangladesh					
40/M Dhaka	Single, well demarcated, oval plaque with a few crusts on the lower part of chest wall	Demonstration of characteristic yeast form in KOH preparation of biopsy	Itraconazole 200 mg daily for three months	Cured	Bhuiyan *et al.* (2015) /Authentic
Cases from Nepal					
60/F imported case (a Nepalese immigrant in USA)	Pulmonary infection, multi-lobular consolidation and foci of necrosis in the lung, followed by a necrotic ulcer on the dorsum of the tongue, h/o Coombs- positive autoimmune hemolyticanemia, and diabetes mellites. Case diagnosed in USA after the patients 9 months stay in Nepal.	Broad-based budding yeast cells in PAS and GMS- stained tissue sections of a transbronchial biopsy and recovery of *B. dermatitidis* from tongue ulcer, BAL fluid and bronchoscopic biopsy	Oral itraconazole for 12 months	Cured.	Gandhi *et al.* 2015 / Authentic

CONCLUSION:

Blastomycosis primarily acanine disease and occurs in dogs about ten times more in humans than that in dogs The review by Randhawa *et al*. (2013 mentioned only one case of can in blastomycosis from India, manifesting as pulmonary infection in a Mongrel dog found dead in Bareli, Uttar Pradesh. Human cases of blastomycosis covered in our review originated from several distant locations in India, Blastomycosis is primarily a canine disease (Schwartz *et al*., 2018) Surveillance for more canine cases in several parts of India and other countries in the Indian subcontinent may facilitate detection of endemic foci of *B. dermatitidis* for human and animal infections. Possibly many more human cases of blastomycosis exist that have not been recognized. A recently developed real-time PCR for identification of *B. dermatitidis* in culture and tissue and antigen testing in broncho-alveolar fluid (Bal), serum and urine is also useful for diagnosis of Blastomycosis (Sidamonidze *et al*., 2012; Linder *et al*.,2021)

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CONFLICTS OF INTEREST:

We have no conflict of interest in this research.

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