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Ustilaginales (Smut Fungi) and their Role in Causing Human Infections, an Update

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ABSTRACT

Ustilaginales is also known as smut fungi are a vast and diverse group of fungi that cause disease in crops causing huge losses worldwide. They belong to the class Ustilaginomycetes. Several members of this group serve as valuable models for unraveling the fundamental mechanisms controlling important biological processes. Several plant pathogenic species of ustilaginales are known to cause human infections. A brief description is given of the genera that contain species pathogenic to humans. The life cycle of *Mycosarcoma* (Ustilago) *maydis* is briefly described. The phenomenon of dimorphism in *Mycosarcoma maydis* is discussed in comparison to a plant pathogenic fungus, *Taphrina deformans*. *Mycosarcoma maydis* was the first plant pathogenic fungus known to cause human infection in a 31-years old corn farmer. There are over twenty species of ustilaginales implicated in human infections. This paper reviews the infections caused by *Mycosarcoma* (Ustilago) maydis, *Psudozyma* species, viz. *Psuedozyma aphidis*, *P. antartica*, *P. parantarctica*, and *P. thialandica*, and *Dirkmeia churashimaensis*.

Keywords: Ustilaginales, Plant, Human pathogenic species, *Mycosarcoma maydis*, and Dimorphism.

INTRODUCTION:

True fungi are a very diverse group of organisms with 1, 4800 described species, and the estimated number is 2.2-3.8 million species with diverse ecological niches and immense economic importance (Hawksworth & Lücking, 2017). The fungi comprise seven phyla: Chytridiomycota, Blastocladiomycota, Neocallimastigomycota, Microsporidia, Glomeromycota, Ascomycota, and Basidiomycota. Ustilaginales belong to the Phylum Basidiomycota, Subphylum Ustilaginomycotina, Class Ustilaginomycetes, subclass Ustilaginomycetidae, Ustilaginales comprise 8 families, 49 genera, and 851 species (Kirk *et al*., 2008). They mostly infect angiosperms, often causing diseases of economic importance, especially in cereals, and form masses of dark, powdery spores in the leaves, stems, flowers, or fruits of the host plants (Allaby, 2013). Ustilaginales cause smut of many cereal grains, including wheat, barley, corn, and rice; masses of spores (sori) are usually black and dusty; basidial apparatus consisting of thick-walled teleutospore (probasidium), which upon germination gives rise to a septate or non-septate tube (metabasidium) bearing teliospores also known as chlamydospores (Martinez-Espinoza *et al*., 2002) Several species of this group serve as excellent models for studying mating, morphogenesis, sign, DNA signal transduction, nycoviruses, DNA recombination, pathogenicity, and genomics (Martinez-Espinoza *et al*., 2002; Wang *et al*., 2015; Kruse *et al*., 2017).

Important plant pathogenic species include Ustilago nuda causing smut of barley (*Hordeum vulgare*). *Ustilago maydis*, causal agent of corn smut is now classified with a new generic name as Myosarcoma maydis (Taggart *et al*., 2016). Human infection caused by a novel pathogen *Dirkmeia churrashimaensis* has been very recently described (Hu *et al*., 2021). This species was formerly identified as a novel *Pseudozyma* species on the basis of morphological and physiologic aspects and by molecular analysis of the D1/D2 domains and internal transcribed spacer (ITS) regions (Hu *et al*., 2021). This species formerly known as *Pseudozyma churashimaensis* is known to produce glycolipid biosurfactants, mannosylerythritol lipids but it has so far not been known to cause a plant disease (Morita *et al*., 2011). Two new species of *Pseudozyma, viz. P. parantarctica and P. thailandica* have also been described (Sugita *et al*., 2003).

During the past six decades, numerous cases of human infections with a varying clinical spectrum caused by a great variety of plant pathogenic fungi belonging to several taxonomic groups have been reported worldwide (Nucci & Anaissie, 2007; Pastor & Guarro, 2008; Gauther and Keller, 2013; Revankar & Sutton, 2010, de Hoog *et al*., 2019). There has been an earlier review of human infections caused by plant pathogenic fungi including ustilaginales (Gugnani *et al*., 2021).

Brief descriptions of genera that have species pathogenic for humans - Ustilago: It is basidiomycetous yeast that inhabits the soil and plant material. It is a pathogen of seeds and flowers of cereals, wheat, corn, and grasses. There are only a few reports of human infections caused by Ustilago. Species of Ustilago grow slowly on agar media as moist, cream to yellow-colored and yeast-like colonies becoming wrinkled and membrane-like with profuse budding in the medium within 20 days (Martinez-Espinoza *et al*., 2002). Microscopically spindle-shaped, elongate, and irregular blastoconidia consisting of spindle-shaped cells are observed. Pseudohyphae and short true hyphae with clamp connections may occasionally be present (Martinez-Espinoza *et al*., 2002). *Ustilago maydis* is a host-specific pathogen, being the causal agent of common smut or "huitlacoche" in maize (*Zea mays*), and its possible ancestor, teozintle (*Zea mays* ssp. *parviglumis* and ssp. *mexicana*). Nevertheless, in contrast to other Ustilaginales that are responsible for severe epiphytics in important harvests, *U. maydis* infections are sparse infecting a low number of corn plants (Martinez-Espinoza *et al*., 2002; Wang *et al*., 2015). Curiously infected ears are edible, and extremely appreciated as a delicacy in México, and in modern international cuisine (León-Ramírez *et al*., 2014). The first three records of human infection caused by Ustilagomyadis (now called *Mycosarcoma maydis*) were from Hungary (Randhawa *et al*., 1959), U.S.A. (Moore *et al*., 1946), and India (Randhawa *et al*., 1959), *Mycosarcoma* (Ustilago) *maydis* is also known to cause respiratory allergy and mycotoxicois (Wołczańska & Szysz, 2018), cases of these diseases will not be described in this review as it deals with infections. *Dirkmeia* (*Pseudozyma*) *churashimaensis* has been used as a leaf colonizing agent for systemic defense of pepper against bacterial and viral pathogens (Lee *et al*., 2017). Human pathogenic species of ustilaginales include *Myosarcoma* (Ustilago) *maydis*, *Psueudozyma phidis*, *P. antartica*, *P. parantarctica*, *P. thialandica* and *Dirkmeia churashimaensis*. Very recently, a cluster of 12 cases of fungemia in pre-term neonates caused by *D. churshimaensis* among NICU patients in a multispecialty hospital in Delhi, India has been described (Chowdhary *et al*., 2020). The authors used whole-genome sequencing (WGS) and amplified fragment-length polymorphism typing and matrix-assisted laser de-sorption/ionization time-of-flight mass spectrometry by using Biotyper 3.1 to understand the genetic relatedness of the isolates and to identify them as *Dirkmeia churanshimaensis*

The present study describes the details of clinical features of some of the cases not given in this review and provides a further update of human infections caused by different plant pathogenic species of ustilaginales, and human infections caused by *Dirkmeia churashimaensis*.

RESULTS:

The literature search revealed many reports of human infections caused by several species plant pathogenic ustilaginaceous fungi belonging to the genera *Myosarcoma*, *Psudozyma*, *Moesziomyces*, and *Dirkmeia* in different countries. A noteworthy observation was the report of a case of human infection due to *Moeszio-*

myces bullatus (formerly called *Pseudozyma bullatus*) from Nigeria (Okolo *et al*., 2015), constituting the first world record of human infection caused by this species. Two new species of *Pseudozyma*, viz. *Pseudozyma antarctica* and *P. thailandica* were found to have been discovered in 2003 (Sugita *et al*., 2003), Sequencing of the internal transcribed spacer 1 (ITS1)-5.8S-ITS2 region of the rRNA gene was used in the identification of some fungi in some of the publications covered in this review (Wang *et al*., 2015; Kruse *et al*., 2017; McTaggart *et al*., 2016; Chowdhary *et al*., 2020; Okolo *et al*., 2015).

DISCUSSION:

The literature search revealed data on human cases of infections caused by different species of ustilaginales in India, Pakistan, China, Japan, the US, Hungary, and Nigeria. The Nigerian case caused *M. bullatus* constituted the first world record of human infection caused by this species This species is also reclassified as *A. thaliana* (The yeast form of *M. bullatus* is known to infect grasses and leaves flowers and fruits of other plants (Eitzen *et al*., 2021) It may be relevant to mention that the case of brain tumor due to *Mycosarcoma maydis* reported by Randhawa *et al* in 1959 from Delhi, India was the first world record of human infection caused by a plant pathogenic fungus.

Table 1: Demographic and salient clinical features of human infection caused by different species of Ustilaginales.

Age/ Sex	Location	Lesion (s) caused	Basis of diagnosis	Treatment	Reference
31/M	Hungary	Dermatomycosis in a corn farmer- infiltrated, hyperpigmented patches on chest, back, arms, inguinal region, and legs, scaly plaques in the axillae, on the neck, elbows, and dorsum of the feet, and scattered red papules on the chest, legs, and buttocks.	Microscopic examination of scrapings from the lesions showed spores, resembling the ones seen in the black smutty rain.	Not known	Preininger & Durch, 1937
55/M	U.S.A.	Leptomeningitis and epididymitis with symptoms of staggering, nausea, slight headaches, and attacks of vomiting of 2 years duration.	Cerebral craniotomy without biopsy led to a diagnosis of chronic cystic arachnoiditis.	After cerebral craniotomy, the patient felt well and returned to doing his chores including husking of corn.	Moore *et al*. 1946
13/F	Delhi, India	Brain tumor with chief symptoms of headache, loss of vision, and sense of smell	Histological examination of biopsy from the brain lesion revealed septate hyphae (6-8.5x1.5-4.8 µm) branching below the septa, occasionally dichotomously with the occasional presence of round and oval fungal bodies. Cultures of the nasal blood originating from the brain yielded.	Not known	Randhawa *et al*., 1959
17/M	Pakistan	Onychomycosis	Not known	Not known	Bokhari *et al*., 1999
23/M	Singapore	Dermatomycosis- Annular, erythematous patches, plaques on the chest wall, knee, and over nasal alae.	Not known	Not known	Teo & Tay, 2006
7/F	U.S.A.	CVC infection with a one-week history of intermittent fevers, chills, malaise accompanied by fatigue. h/o gastroschisis and ileocolonic resulting in short bowel	Intravenous fluconazole loading dose of 10 mg/kg-1 followed 24 h later by a 5 mg kg−1 per day	The patient recovered after Itraconazole. Replacement of the maintenance	Lin *et al*., 2008

		syndrome.	maintenance dose for 5 days.	does with itraconazole for 10 days.	
3/M	USA	Abdominal pain, vomiting, and diarrhea. He had a very complex medical history-three episodes of infectious peritonitis with *Candida parapsilosis* (3.5 yrs. prior), *Staphylococcus epidermidis* (3 yrs. Prior), and Group A Streptococcus (1.5 yrs. prior), end-stage renal disease, and hypertension secondary to posterior urethral valves and obstructive uropathy and chronic peritoneal dialysis. He later had a persistent fever.	The fungus isolated from peritoneal culture on SDA produced very mucoid colonies and was misidentified as Cryptococcus. Sequencing of the DNA of isolate at University of Texas Health Center at San Antonio identified it as belonging to the genus Ustilago; the culture lost its viability for further identification.	Initial treatment with fluconazole on hospital day 7 replaced 21 with liposomal amphotericin B mg/kg/dose intravenously. With intermittent hemodialysis and initiation of peritoneal dia-lysis the patient was doing well.	McNeil & Palazzi, 2012
51/M	China	Coinfection With *Nocardia otititidis-caviarum*- Chronic mycetoma of the leg with multiple discharging sinuses for 25 years in a farmer	Histopathology revealed grains in H & E-stained tissue sections and clustered yeast cells in PAS-stained tissue sections.	Not known	Chen *et al*., 2011
Age & Sex?	Tokyo, Japan	Spontaneous pneumothorax (coinfection with *P. parantarctica*, *P. thialandica*)	Blood cultures yielded the three species. Identification was based on a detailed study of microscopical features. The isolate of *P. antarctica* was identified by rDNA sequence analysis. The other two were identified as new species.	The isolates were resistant to 5-flucytosine, and *P. thailandica* was also resistant to fluconazole. No treatment was given, an outcome not mentioned.	Sugita *et al*., 2003
32/F	Jos, Nigeria	Neonatal sepsis with several complications. Requiring blood transfusions, administration of antibiotics, and phototherapy.	Direct microscopic examination revealed the presence of septate hyphae. Identification of the isolate as *M. bullatus* was done by sequencing of the internal transcribed spacer 1 region of the rRNA gene.	The infant died on 32 days of her life.	Okolo *et al*., 2015
80/F	Nanchang, China	Subcutaneous fungal granuloma-an egg-shaped plaque of 2 years duration on the extensor side of her left forearm with slight pain, near the wrist joint. The lesion slowly spread to the surrounding region. Papules, plaques, and nodules developed successsively, with exudation and ulcers appearing on the lesion surfaces. Examination showed a 14 x 9 cm irregular, infiltrated erythema tous plaque with a distinct margin on the extensor side of her left forearm. Varying nodes, and scales could be observed within the involved region. There was no history of trauma or systemic disease.	Demonstration of fungal spores and conidia in the direct 10% KOH. Examination of skin biopsy. PAS and GMS-stained tissue sections showed Blastoconidia. Based on in vitro susceptibility tests the patient has treated with oral itra-conazole 0.2 mg twice a day. Three months of treatment, all the lesions were almost completely cured, & no new lesions were seen.	The itraconazole dose was reduced to 0.1 mg. Day for 5 months. The lesions healed completely after another month of treatment, In the 1-year follow-up examination, the patient was free of symptoms.	Hu *et al*., 2021

Meaning of medical terms and abbreviations

Dermatomycosis: Fungal infection of the skin; Leptomeningitis: Inflammation of the pia mater and the arachnoid membrane of the brain; Cystic arachnoiditis: Fluid-filled sacs that occur on the arachnoid membrane that covers the brain and the spinal cord, Ependymitis: Inflammation of the cerebral ventricular system; Cerebral craniotocasesmy: a surgical procedure in which a part of the skull is temporarily removed to perform an intracranial procedure

CONCLUSION:

A noteworthy finding in our review was the report of a cluster of 12 cases of fungemia in pre-term neonates caused by D. churashimaensis among NICU patients in a multispecialty hospital in Delhi (Chowdhary *et al*., 2020), constituting the first known record of human infection due to this fungus; Another noteworthy observation in our literature search was a case of mycetoma in 51 yrs-old male in China caused by coinfection of *Pzeudozyma aphdis* and *Nocardia oititidiscaviarum* (Chen *et al*., 2011). Cereal crops likely maize, wheat, barley, pearl millet are often infected with smut fungi, which may cause infection in persons encountering these plants. Thus, there is a need for surveillance of the occurrence of infections in supervisory staff and workers engaged in the cultivation of these crops.

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CONFLICTS OF INTEREST:

I have no conflict of interest with any individual or organization

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