

## Original Article

# Clinical spectrum and outcome of invasive filamentous fungal infections in children with Type 1 diabetes: North Indian experience

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**Abstract.** There is scarcity of data on spectrum and outcome of invasive filamentous fungal infections (IFIs) in children with Type 1 diabetes (T1D) from developing countries. A retrospective review of medical records of children with T1D hospitalized with IFI over the past decade at the Pediatric Endocrinology and Diabetes Unit of a large tertiary care hospital of North India was performed with an aim to study their clinical spectrum, hospital course and final outcome. Of the 10 patients studied, nasal/paranasal involvement was seen in 6 and pulmonary involvement in 5 patients. One patient developed disseminated disease. Majority of the identified mycoses belonged to Class Zygomycetes Order Mucorales. Early surgery along with antifungal therapy helped limit the extension of infection and achieve a good outcome in majority of patients. Two patients died; one with a late diagnosis of pulmonary mucormycosis and the other with disseminated disease. The longterm morbidity in the survivors was minimal. In conclusion, rapid diagnosis followed by a multimodal approach involving aggressive surgical debridement, appropriate antifungal therapy and control of hyperglycemic state is the key to good outcome in this otherwise lethal infection.

**Key words:** Type 1 diabetes, children, invasive fungal infections, filamentous, zygomycosis

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## Introduction

Diabetes mellitus may predispose individuals to invasive fungal infections (IFI) probably related to impaired functions of neutrophils, macrophages, cellular and humoral immunity, and iron metabolism (1, 2). Children with Type 1 Diabetes (T1D) who present with ketoacidosis have increased susceptibility to infections partly due to the acidic environment that is ideal for certain pathogens including invasive fungi (1, 3). Majority of the IFIs in children with poorly

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controlled T1D and ketoacidosis are caused by Zygomycoses and are invariably fatal without aggressive management (4). The key to good outcome is fast and accurate diagnosis which is usually difficult to establish due to non-specific clinical symptoms and signs and the need for invasive diagnostic procedures for confirmation of IFI (4, 5). The treatment is often challenging as it involves extensive surgical debridement of involved tissues in addition to antifungal drugs (4). The outcome is generally poor in resource constrained setups like ours but is gradually showing improvements (6, 7). The data on outcome of IFIs in children with T1D is scarce and is almost confined to invasive zygomycosis (4). With an aim to determine the clinical spectrum and final outcome of children diagnosed with T1D and IFI over the last decade at our hospital, we performed a retrospective review of their medical records.

### Patients and Methods

The analysis of hospital data of patients with T1D diagnosed to have a confirmed IFI was conducted at Advanced Pediatrics Center of our Institute which is a tertiary care referral center located in Northwest India and included the period from March, 2004 to February, 2014. All patients were diagnosed as T1D according to The International Society for Pediatric and Adolescent Diabetes (ISPAD) criteria published in 2000 and revised in 2009 (8, 9). The diagnosis of associated fungal infection was based on microbiological and/or histopathological examination of tissue specimens. Data related to the basic demographic profile, age at the time of diagnosis, mode of initial presentation like diabetic ketoacidosis (DKA), imaging details, treatment modalities, duration of hospitalization and the final outcome were noted. The Institute's Ethics Committee approved the study.

### Results

Ten patients (6 girls and 4 boys) amongst 524 children with T1D on follow up in Pediatric Diabetes Clinic were treated for various IFIs during the study period. The mean (SD) age of presentation was 9.1 (3.4) yrs (range 3–12 yrs). The median duration of diabetes was 21.8 months (range 0.75–48 mo). The predisposing factors included poor adherence to insulin therapy resulting in poor metabolic control (mean HbA1c  $9.3 \pm 1.2\%$ ) and presence of acidosis in 9 patients and malnourished state in all (mean BMI  $12.6 \pm 1.2 \text{ kg/m}^2$ ). None of the patients showed poor hygiene status. Eight patients were previously diagnosed with T1D while 2 were diagnosed recently. Nine patients presented with DKA. The commonest presenting feature related to fungal infection with suspected rhinocerebral involvement was facial and/or orbital swelling in 5 patients, followed by serosanguineous nasal discharge and ophthalmoplegia. Patients with pulmonary involvement had non-paroxysmal dry cough. Majority of patients had low grade fever at the time of presentation. The most common site of fungal infection was nasal cavity and paranasal sinuses seen in 6 patients; 5 of these were due to mucormycosis while 1 had aspergillus flavus. Sinusitis involved ethmoid sinus in 5 patients and maxillary and frontal sinuses in 4 patients each (Table 1). Lung involvement was seen in 5 patients; 2 of these had pleural and thymic involvement in addition. One patient had disseminated disease involving paranasal sinuses, lungs and gastrointestinal tract.

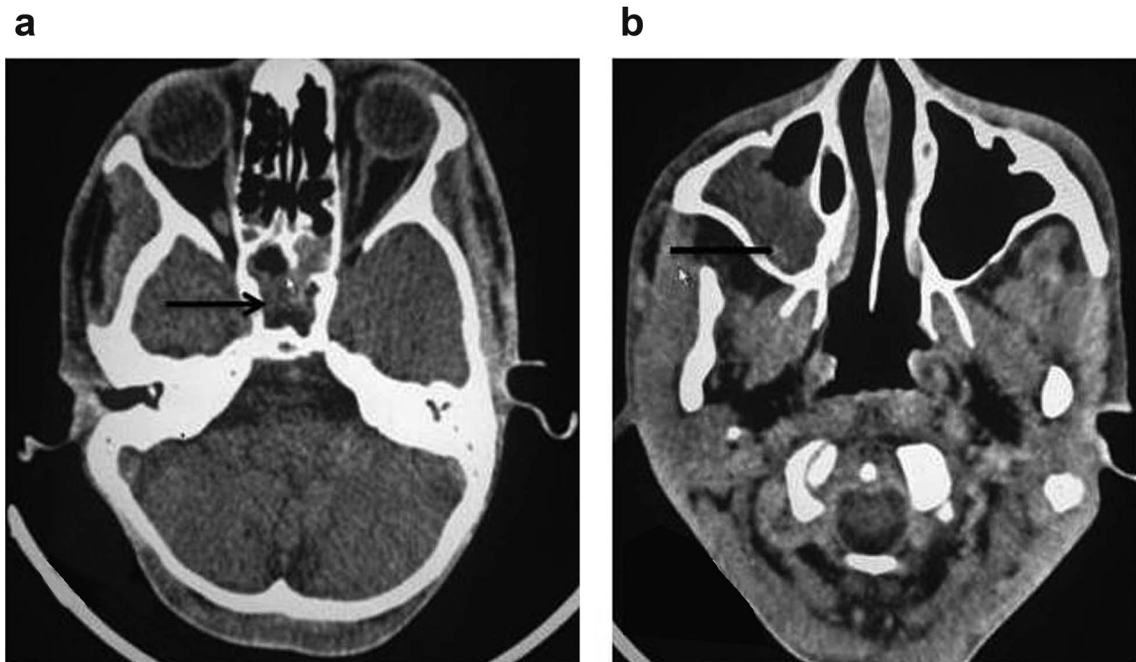
Routine laboratory investigations were unremarkable in majority of patients. All patients showed neutrophilic leucocytosis with mean leukocyte count of  $12.3 \times 10^9/\text{L}$ . Radiological investigations included contrast enhanced computed tomography (CECT) scans of suspected involved sites in all patients. Paranasal sinus involvement was documented in 6 patients (Fig. 1a and b); 2 of these had orbital extension. Intracranial extension predominantly

**Table 1** Clinical and laboratory profiles, treatment modalities and outcome of the study cohort

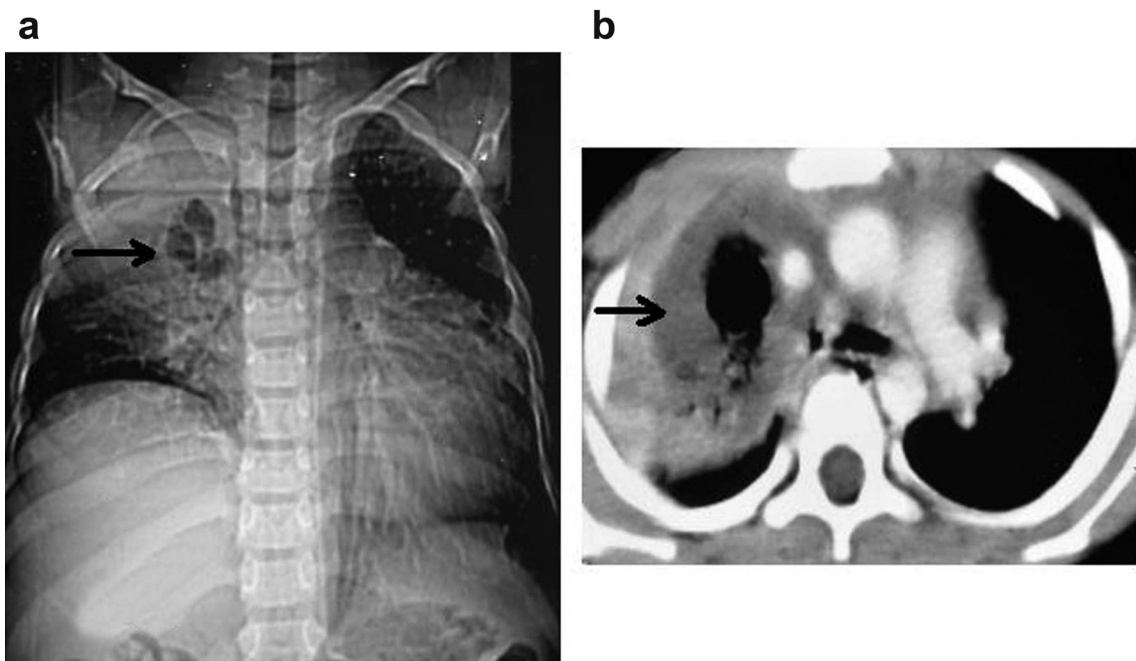
Subject no	Age (yrs)/sex	Presenting features	Sites involved	Imaging findings	Days to confirm IFI
1	11/M	DKA, altered sensorium, dry cough, fever	Rt. lung	Cavitatory pneumonia rt. upper & middle lobe	14
2	5/M	DKA, altered sensorium, low grade fever	Lt maxillary, ethmoid & frontal sinuses, brain	Opacities in lt. maxillary, ethmoid & frontal sinuses, frontal lobe abscesses	7
3	12/F	DKA, altered sensorium, chest pain, fever	Lt. lung, pleural cavity	Cavitatory pneumonia lt. lower lobe, left empyema	5
4	12/F	DKA, altered sensorium, dry cough, low grade fever	Lungs, thymus	Thymic abscess, rt. upper lobe consolidation	7
5	12/F	DKA, orbital swelling, nasal discharge	Rt. ethmoid & bilateral maxillary sinuses	Soft tissue density lt. nasal cavity, rt. ethmoid & bilateral maxillary sinuses	3
6	10/F	Fever, mild dry cough, osmotic symptoms	Rt. lung	Cavitatory pneumonia, mediastinal & hilar lymphadenopathy	14
7	5/M	Fever, altered sensorium, lt. orbital swelling, DKA	Lt. maxillary sinus and orbit, brain	Lt. maxillary sinus mass with orbital extension, lt. frontal lobe cerebritis	2
8	3/M	DKA, black discoloration of nose following trauma, nasal discharge, facial swelling	Nasal vault, lt. Maxillary & ethmoid sinuses	Opacities in lt. maxillary and ethmoid sinuses	1
9	10/F	Fever, Rt. Ear discharge, facial swelling, proptosis, ophthalmoplegia, altered sensorium, DKA	Disseminated disease involving paranasal sinuses, lungs & Gastrointestinal tract	Soft tissue mass rt. frontal & bilateral ethmoid sinuses with blocked osteomeatal complex	2
10	11/F	DKA, head trauma, scalp wound, swelling of scalp & upper face	Scalp, ethmoid & frontal sinuses, orbit	Opacities in rt. frontal & ethmoid sinuses	3

Subject no	Confirmatory test	Organism(s)	Treatment	Hospital stay (days)	Outcome	Follow up
1	Histopathology of postmortem lung biopsy	Mucor	Ampho B	14	Died	–
2	Histopathology of debrided tissue from sinuses	Mucor	Ampho B, extensive debridement of sinuses and excision of cerebral abscesses	48	Recovered Asymptomatic	9 yrs
3	Pleural fluid aspirate Histopathology of lung tissue	Mucor	Ampho B, resection of lt. lower lobe & lingula, pleural lavage	45	Recovered Mild pulmonary dysfunction	8.5 yrs
4	Smear of thymic aspirate	Mucor	Ampho B, excision of thymic abscess & affected rt. upper lobe	70	Recovered Asymptomatic	6 yrs
5	Smear of nasal scrapping Histopathology of debrided sinus tissue	Mucor	Ampho B, lt. rhinotomy, rt. external ethmoidectomy, debridement of maxillary sinuses	16	Recovered Asymptomatic	6 yrs
6	Histopathology of lung biopsy	Mucor	Liposomal ampho B	60	Recovered Asymptomatic	3.5 yrs
7	Histopathology of debrided sinus tissue, cultures	Rhizopus	Ampho B, sinus debridement surgery	2	Left Against Medical Advice	–
8	Smear of nasal scrapping and histopathology of debrided sinus tissues	Mucor	Ampho B, debridement of necrotic tissue of nasal vault & sinuses	42	Recovered Asymp- tomatic	1 yr
9	Histopathology of debrided tissue from sinuses Histopathology of tissues on autopsy	A. flavus C. glabrata	Ampho B/voriconazole, sinus debridement surgery	30	Died	–
10	Smear & histopathology of debrided scalp tissue	Mucor	Ampho B, extensive debridement of necrotic tissue of scalp & upper eyelids, debridement of nasal & paranasal spaces	90	Recovered, Facial disfigurement currently undergoing staged repair	9 months



**Fig. 1.** a: Soft tissue opacities in frontal and ethmoid sinuses with blocked osteomeatal complex.  
b: Opacification of right maxillary sinus.



**Fig. 2.** a & b: CECT chest showing cavitary pneumonia on right side.

involving frontal lobes was seen in 2 patients. The commonest pulmonary CECT appearance was that of cavitary pneumonia (Fig. 2a and

b); 1 patient, described elsewhere, showed empyema in addition (10). Another patient had necrotic thick walled abscess in the thymus with

consolidation of apical segment of right upper lobe and small subpleural nodular lesions in the right lower lobe (11).

Confirmation of diagnosis by direct microscopy of specimen (smear/aspilate) was made in 1 patient, by histopathological examination in 5 patients and by both techniques in 4 patients. Culture on Sabouraud dextrose agar grew *Rhizopus microsporum* (*Rhizopodiformis*) in 1 patient. The most common yield was from smear or histopathological examination of tissues obtained at the time of surgical debridement of paranasal sinuses. In 2 patients who had serosanguineous nasal discharge the diagnosis was made from smear of nasal scrapings. The identified etiological fungi belonged to the order Mucorales in 9 cases (1 further identified as *Rhizopus microsporum*) and *Aspergillus flavus* in 1 patient. The mean time from presentation to diagnosis was  $5.8 \pm 4.7$  days (range 1–14 days).

All patients were treated with either intravenous amphotericin B (conventional or liposomal) or voriconazole for a targeted duration of 4–6 weeks. Surgical intervention was done in 8 patients and included debridement of paranasal sinuses by either endoscopy or external approach in 5, excision of brain abscesses in 1, resection of affected lung areas in 2 and excision of thymic abscess in 1 patient.

The average time to resolution of DKA was 18.6 hrs. Mean duration of hospital stay was  $41.7 \pm 27.2$  days (range 2–90 days). Two out of 10 patients died; 1 with pulmonary mucormycosis suffered massive hemoptysis on day 14 of hospitalization while the other with disseminated aspergillosis died of a large bout of hematemesis and showed an intestinal perforation on autopsy. All survived children have remained well over a mean duration of  $4.96 \pm 3.3$  yrs (range 9 mo–9 yrs) in follow up except 1 who continues to show mild restrictive pattern on pulmonary function tests.

## Discussion

Invasive mycoses are uncommon but often lethal infections that disproportionately affect T1D patients with poor metabolic control (2, 3). Poor adherence to insulin therapy, malnourished state and episodes of ketoacidosis particularly predispose children with T1D to develop IFIs (2, 3, 11, 12). Majority of our patients had all these critical factors required for development of IFIs. Poor glycemic control may result in dysfunctions of macrophage phagocytosis, neutrophil chemotaxis and oxidative killing (1), and ketoacidosis may induce a temporary block in binding of iron to transferrin providing free iron which enhances growth of many IFIs particularly mucormycosis (2, 13, 14). Poor compliance to therapy as evidenced by poor clinic attendance, risk taking behaviors and recurrent admissions for DKA has been documented to increase susceptibility to IFIs (12). Similarly malnourished state resulting either from a poor glycemic control or poor dietary management predispose diabetic children to IFIs (3, 10–12). The presence of critical predisposing factors and an unusually high occurrence of IFIs in our patients is probably a result of the prevailing healthcare situation related to the management of T1D in children in our setup (15). Late diagnosis of diabetes due to lack of awareness of parents and the primary healthcare physicians is common in India (15). Children are often diagnosed only when they have developed ketoacidosis (16). Poor metabolic control is also common due to lack of comprehensive diabetes care (15, 17). There are only a few specialized centers and majority of the patients are treated by the primary care physicians who have limited knowledge about the disease and the modern treatment options (15). Additionally, poor socioeconomic status often makes even the conventional insulin therapy and blood glucose monitoring unaffordable by the parents (15). The prevention of IFIs in children with T1D requires early diagnosis of diabetes before onset of ketoacidosis, meticulous

glycemic control in follow up and good nutritional management. Improvements in diagnosis and care of children with T1D in our country setup will probably lower the incidence of IFIs in these patients in future.

Establishment of an early diagnosis of IFI is important but is often difficult due to absence of specific symptoms (5). We believe that a high index of clinical suspicion in a setting of predisposing risk factors present in our patients resulted in rapid establishment of diagnosis. Presence of subtle clinical features like dry cough, tachypnea persisting after resolution of acidosis, facial swelling, serosanguineous nasal discharge and low grade fever in poorly controlled, malnourished children who present in ketoacidosis are pointers to the presence of IFIs (5, 11, 12). In patients suspected to have rhinocerebral involvement, smear examination of scrapings from nasal or sinus cavity are useful aid to rapid diagnosis. The diagnosis of pulmonary IFI is highly probable if the CT scan shows cavitory pneumonia in a child with minimal pulmonary symptoms and previously described risk factors (10). Fine needle aspiration cytology can be very useful in reaching an early diagnosis of pulmonary IFIs as compared to more invasive transbronchial biopsy (10, 18).

The cornerstone of management is a combination of antifungal drugs and early surgical debridement of involved tissues that may prevent extension of infection to the surrounding areas (4, 19). Treatment with antifungals alone is usually ineffective due to poor concentrations in affected tissues resulting from vascular invasion, thrombosis, occlusion and infarction (4). In our patients who had rhinosinusitis, early surgical debridement probably prevented a contiguous extension of infection into the brain. The only patient who required excision of brain abscesses had received a late diagnosis. One of the 2 patients who received only antifungal therapy died; the survivor received liposomal amphotericin B which had been previously reported to be able to achieve cure even in the absence of associated

surgery (20). The success rates of a multimodal treatment approach in our study are similar to those achieved across many centers around the world (4, 5, 19). The long term morbidity related to consequences of the fungal disease was also minimal and confined to the sequelae of tissue loss from radical surgeries.

In conclusion, rapid and accurate diagnosis of IFIs in children with T1D and a multimodal management approach involving early surgery, appropriate antifungal therapy and control of hyperglycemic state is successful in achieving a good outcome. To the best of our knowledge, ours is the largest single center data and the first study from a developing country setup on IFIs exclusively in children with T1D.

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