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Gastrointestinal Mucormycosis in a two-year-old child: A clinical and radiological enigma

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ABSTRACT

Mucormycosis is a rare, fatal angioinvasive infection occurring in immunocompromised individuals. Gastrointestinal mucormycosis is rare variety with high mortality rate. We present a case of GI mucormycosis in a 2-year-old male child who presented with abdominal mass with no underlying risk factors. The aim of this case report is to emphasize on its etiopathogenesis and keeping mucormycosis high in the differential diagnosis in a child presenting with abdominal mass.

1. Introduction

Mucormycosis (MM) is an uncommon, fatal, angioinvasive opportunistic fungal infection which can affect any organ system [1]. Rhino-orbital-cerebral and pulmonary infections are the most common types of MM [2]. Gastrointestinal (GI) involvement is a rarer variety, affecting stomach, colon and ileum and accounts for 4%–7% of all cases [2]. GI Mucormycosis is associated with very high mortality of about 85% [2]. It usually affects premature and low birth weight neonates with usual clinical presentation of abdominal pain, distention, bloody diarrhoea and perforation [3]. Very rarely does a fulminant infection like Mucor present as abdominal mass mimicking a neoplasm. We describe a two-year-old male child who was misdiagnosed both clinically and radiologically as primary GI lymphoma with metastasis to liver but on histopathology was confirmed as MM. The case holds its importance in highlighting the atypical presentation of this potentially lethal, however treatable condition amongst clinicians and radiologists who must keep gastrointestinal MM high up in the differential diagnosis for abdominal masses especially in toddlers. An attempt to discuss detailed pathogenesis and impress upon the newer modalities for establishing a rapid diagnosis has also been made.

2. Case

A two-year-old male child presented to Pediatric surgery out patient department on day 0 (day of admission) with complaints of recurrent abdominal pain, progressive abdominal distention for past two weeks and multiple episodes of non-bilious vomiting with persistent pain in the abdomen for past three days. No significant past or family history was present. The child was full term at birth and delivered vaginally. He was fully immunized for age and had normal developmental milestones. Physical examination revealed pallor with no lymphadenopathy/icterus/pedal edema. The weight for age and length for age was less than 5th percentile, indicating the child was severely malnourished. There was moderate hepatomegaly with a non-tender lump felt per abdomen. On day 0 his haemoglobin was 6.6g/dl. RBC count- 2.26 million/cumm, MCV- 89Fl, MCHC- 32.8 pg, TLC- 18,200/cumm, DLC showed neutrophilia and platelet count was 30,000/cumm. The liver function tests were mildly deranged and CRP was high (211mg/L). Despite low hemoglobin, his serum iron levels were borderline high (130 μg/dl). Other systemic examinations were within normal limits. X-ray abdomen showed a loaded colon suggestive of intestinal obstruction. Ultrasonography (USG) abdomen showed distended bowel loops with sluggish bowel movements along with hypoechoic lesions with satellite lesions in VI and VII segments of liver; suggestive of hepatic hemangioma on day +1. On day +2, the Contrast Enhanced Computed Tomography (CECT) abdomen was done for confirmation which revealed an ill-defined multifocal hypodense lesion of size 8 × 6.5 × 4.6cm in the right lobe of liver (Fig. 1a). There was also presence of circumferential thickening of wall in the jejunum and ileum forming a large mass with dilation of proximal loops (Fig. 1b). A similar hypodense lesion was also seen in right side colon (Fig. 1c). In view of the CECT findings and clinical presentation, a provisional diagnosis of primary bowel lymphoma with metastasis to liver was made. On day

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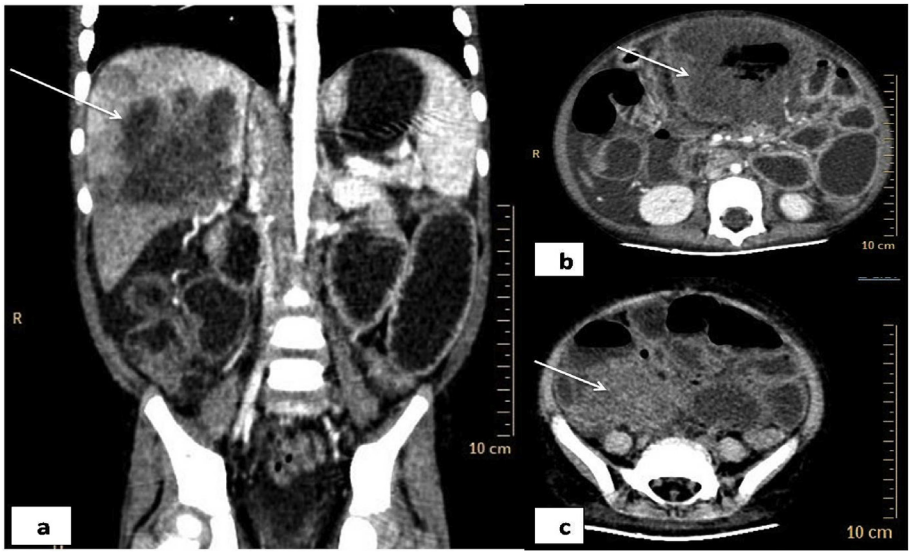

Fig. 1. Fig. 1a: CECT abdomen showing an ill-defined multifocal lesion in the right lobe of liver. Fig. 1b: Showing a circumferential thickening of jejunal and ileal wall. Fig. 1c: Showing a hypodense lesion in the right sided colon.

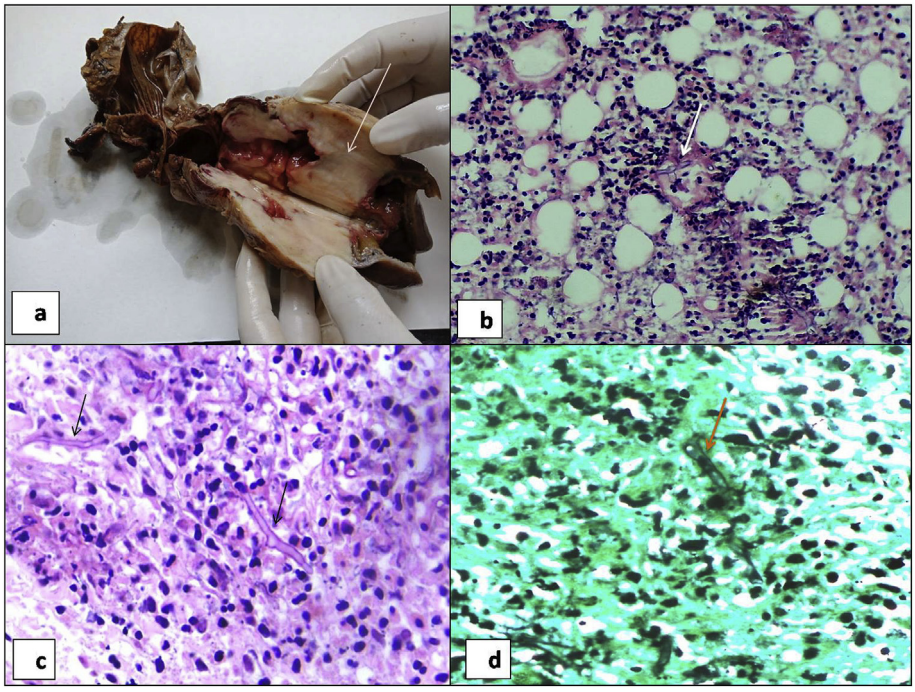

Fig. 2. Fig. 2a: Intestinal segment showing a mass lesion involving the wall causing luminal narrowing. Fig. 2b: Microscopy showing florid inflammatory and fibroblastic reaction with presence of broad aseptate hyphae. Fig. 2c: Necrosis with multiple fungal hyphae. Fig. 2d: Silver Methenamine highlighting Mucor.

+4, the patient developed obstruction and was taken up for exploratory laparotomy. Per operatively, two masses were seen involving the jejunum and right sided colon with dense adhesions to the surrounding intestine. The colonic mass was excised to relieve the obstruction and sent for histopathological examination. Postoperatively, the patient was transferred to pediatric intensive care unit where he showed rapid deterioration. Despite good intensive care management, he succumbed to death due to multiorgan failure on day+5. Gross examinational of the intestinal segment (14cm length) showed a mass in the serosa densely adhered to adjacent loops of intestine measuring 7 × 5 × 3.5 cms and involving the intestinal wall circumferentially causing luminal narrowing (Fig. 2a). The mass was firm, grey white with foci of haemorrhage and necrosis. Microscopic examination from the mass showed florid inflammatory and fibroblastic reaction comprising of histiocytes, neutrophils, eosinophils, lymphocytes, plasma cells and giant cells along with presence of broad aseptate hyphae showing right and obtuse angle branching (Fig. 2b and c). There was evidence of granulomatous reaction with diffuse areas of necrosis and extensive angioinvasion. The intestinal mucosa showed mucosal gangrene, probably due to ischemia and thrombosis of the vessels. The fungal hyphae were highlighted on Silver Methenamine stain (Fig. 2d). A final diagnosis of invasive gastrointestinal MM was made. The paraffin embedded block was sent for species identification of the fungus by molecular PCR technique butwas reported negative. . Post mortem, the liver mass was not resected or aspirated due to ethical reasons, however the CECT images were reviewed and it was suggested that the hepatic mass could be of fungal origin.

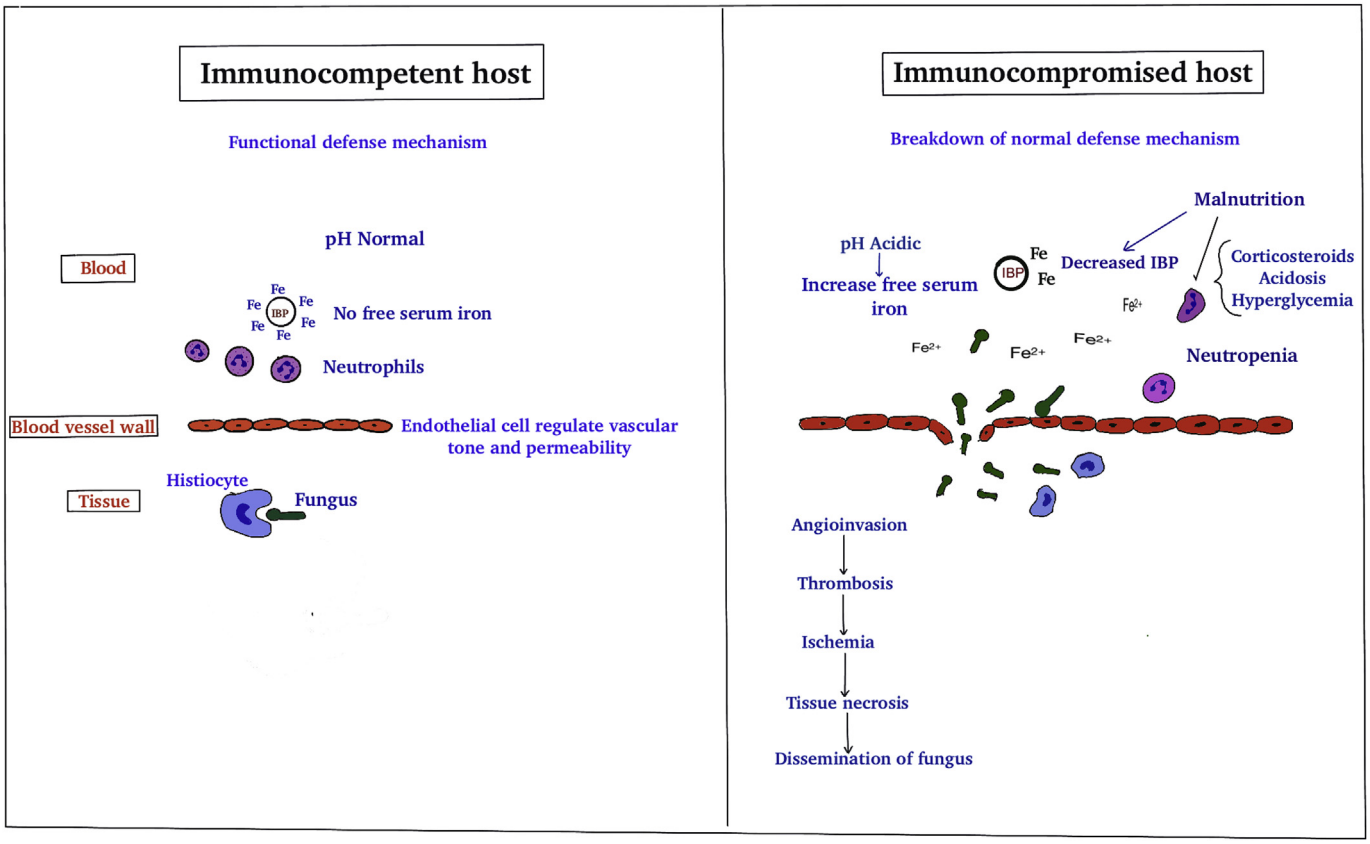

Fig. 3. Etiopathogenesis of Mucormycosis. 3a) In an immunocompetent host, functional defense mechanisms prevent the fungus from establishing infection, multiplication, invasion and subsequent dissemination throughout the body. Circulating neutrophils and histiocytes play an important role. In presence of normal pH, free serum iron (Fe) is sequestered by iron binding proteins (IBP), hence no free Fe is available to support the growth of fungus. Also, the normal functioning and intact endothelial cells regulate the vascular tone and permeability. 3b) In an immunocompromised state e.g., diabetes, corticosteroid therapy and malnutrition, there occurs breakdown of normal defense mechanism. Uncontrolled fungal proliferation occurs owing to neutropenia and functional defects in neutrophils. In addition, decrease in number of IBP occurs in malnutrition which leads to increase in free serum iron. Acidic pH in Diabetic ketoacidosis leads to release of Fe 2 + from IBP. An increase in free iron supports the growth of fungus. The fungus then adheres and damages the endothelial cells leading to angioinvasion, thrombosis, ischemia, tissue necrosis and finally dissemination throughout the body.

3. Discussion

Mucormycosis is a life-threatening angioinvasive fungal infection accounting for 10% of all mycotic infections [1]. Despite intensive use of antifungals and surgical debridement, the mortality rate of these patients continues to be > 40% for many decades [4]. GI Mucormycosis accounts for 4%–7% of all cases with a mortality rate of 85% [2]. Rhizopus arrhizus is the most common organism causing MM [5]. Immunocompromised state is an important risk factor for Mucor. However, in 19% cases no underlying cause was determined of which 9% had GI manifestations [6]. Predisposing factors in young adults include Diabetes, HIV, lymphoma and leukaemia patients on chemotherapy. Malnutrition, prematurity, neutropenia, steroid intake, acidosis and excess iron stores are other important risk factors for infantile MM [3,4]. MM can be acquired by pathogens in food such as fermented porridge, corn, herbs contaminated with spores. On the basis of clinical presentation and anatomical site, MM is divided into six clinical types: (1) rhino cerebral, (2) pulmonary, (3) cutaneous, (4) gastrointestinal, (5) disseminated and (6) miscellaneous (brain, bones, mediastinum, trachea, kidneys) [7]. Majority of children (50%) with GI involvement are infants [7].

Males are more commonly affected than females with M: F = 1.6:1 [7]. In adults, stomach is the most commonly involved site followed by colon, small intestine and esophagus; however, in infants, mostly colon is involved (74%) followed by stomach and ileum (37%), appendix (16%) and extra intestinal involvement in 26% of cases [7]. Till date only five cases of infants with small intestinal MM have been described from the Indian subcontinent [7]. The chief complaints of GI mucormycosis in children are abdominal distention, perforation, pain abdomen and bloody diarrhoea. Rarely does it present as a mass leading to obstruction.

The key factor in pathogenesis of Mucor are host defense mechanisms, fungal endothelial interaction and role of iron (Fig. 3). In individuals with normal immune function, mononuclear and polymorphonuclear cells generate oxidative metabolites which kill Mucorales. This is the reason for neutropenia and dysfunctional phagocytes being risk factors in causing MM. Diabetic patients are at increased risk because impaired glucose levels and ketoacidosis are known to impair phagocytic defence mechanism [8]. The hallmark of MM is extensive angioinvasion, thereby causing vessel thrombosis and tissue necrosis. Endothelial cells cause phagocytosis of dead fungus which leads to further tissue damage. This is the rationale behind the need of surgical debridement along with antifungal therapy to treat Mucor infection. Serum iron level also plays a role in the pathogenesis of MM. Increased serum iron levels raise the susceptibility of MM. In diabetic ketoacidosis, iron is released from transferrin in acidic pH, thus causing predisposition for MM [7].

Diagnosis of MM in GI tract is often delayed due to nonspecific presentations. Considering very high mortality rates associated with the disease, developing a high suspicion and establishing an early diagnosis become imperative for institution of systemic antifungal therapy and surgical intervention. Radiological imaging findings also are

Table 1

Author	Year	Age (years)	Gender	Immune status	Site	Treatment	Outcome
Lin WY et al.	2011	6	Male	Immunocompromised (known case of ALL)	Mass over right lower abdomen	Intravenous liposomal Amphotericin B	Expired post-surgery
Felipe Caino et al.	2016	2	Female	–	Mass adhered to right kidney, caecum and ileum	Surgical debridement, IV Amphotericin B	Expired on day 54
Present case	2019	2	Male	Immunocompetent	Two masses, one in jejunum & other in right sided colon	Surgical debridement	Expired in post-operative period

nonspecific and include bowel wall thickening with adjacent inflammation and spreading to contiguous structures, including the peritoneum [9].

Currently, no antigen detection test for MM is available; however, Galactomannan detection test can be used to rule out invasive aspergillosis, a close differential. Blood cultures are almost always negative.

Histopathological examination of the involved organ provides definitive diagnosis of Mucor. They appear as aseptate, wide, ribbon-like hyphae that branch at right or obtuse angles. Vascular thrombosis is a feature seen in zygomycosis due to angioinvasion by the fungus. Further, they can be highlighted by special stains like Gomori's methenamine silver (GMS) or Periodic acid Schiff (PAS) stains. Sometimes, immunohistochemistry with commercially available ant zygomycete antibodies are also helpful [10]. Fungal culture of the tissue specimen however is the gold standard for diagnosis, as it not only confirms diagnosis but also allows precise genus and species identification. The material taken from biopsies sent for fungal culture should be carefully managed to avoid crushing because these fungi are fragile, and culture may show negative results. Growth is rapid and occurs when incubated for 24 h at 25–37 °C. Nowadays, molecular testing with tissue samples can also confirm the histological diagnosis. Molecular methods based on PCR uses ITS1 and ITS2 regions which are variable between most fungal species as targets for species identification [11]. Other molecular methods are 18S-targeted semi-nested PCR and real-time PCR targeting cytochrome b gene [11]. Kasai et al. have introduced two real time quantitative PCR assays which targets 28S rRNA gene [11]. Since, both histopathology and culture are time consuming processes, promising Molecular Assays have also emerged to identify fungal pathogens and species identification, both from fresh and formalin fixed paraffin embedded (FFPE) tissue. According to a literature, the sensitivity of PCR with FFPE tissue was 56% while sensitivity with fresh tissue was 100%. Formaldehyde fixation causes nucleic acid fragmentation due to extensive cross linkage of tissue protein which inhibits PCR process [12].

Timely diagnosis is essential in Mucor, and in cases with strong suspicion or predisposing factors can be expedited with frozen sections on endoscopic biopsies [13]. Initial imaging studies in GI fungal infections usually lags behind the clinical progression, hence poorly grasped by clinicians. Frozen section along with fresh tissue examination in KOH/Calcofluor-white can help establish a rapid intraoperative diagnosis. According to recent studies use of frozen sections shorten the time of diagnosis and is related to improved outcomes [14].

GI Mucor clinically mimics Necrotising enterocolitis (NEC), though the two entities can be differentiated on radiology and histopathology. In NEC, X-Ray abdomen shows pneumatosis of intestinal wall and USG abdomen shows presence of air microbubbles inside wall thickness as hyperechoic spots. These features are absent in MM. On histopathology, pneumatosis intestinalis (submucosal gas-filled cysts with minimal surrounding tissue reaction) is a characteristic feature of NEC, not seen in Mucor.

Anti-fungal treatment alone is usually insufficient in controlling invasive MM due to factors like resistance to the anti-fungal agents, angioinvasion and thrombosis of vessels which causes less optimal penetration of the medications to the site of interest. Surgery to debulk the fungal infection with resection of all the infected necrotic tissue is often required along systemic antifungal agents [15]. Liposomal Amphotericin B is the preferred agent with favourable toxicity profile, superior CNS penetration and greater efficacy. Salvage therapy is required in refractory disease or polyene intolerance, which includes posaconazole, recombinant cytokines, and granulocyte transfusion or combination therapy. Extensive review of literature has revealed only four case reports of infants in whom an antemortem diagnosis of GI MM was made. All of them were treated by surgical intervention and antifungal therapy but only three survived [7]. In addition, only two case reports have been published in Literature where in the clinical presentation of Mucor in the GI tract was of a mass lesion (Table 1).

To conclude, gastrointestinal involvement by Mucor is not so

uncommon in children. High serum iron levels is an important predisposing factor for Mucor infestation in a otherwise immunocompetent host. Severe malnutrition in addition produces state of immunodeficiency leading to increased risk. . Presentation can be variable with mass lesions mimicking neoplasms. An early diagnosis in such cases will ensure timely management and can drastically reduce the mortality associated with this lethal disease.

Conflict of interest

None.

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None.

References

[1] M.C. Sharma, S.S. Gill, S. Kashyap, R. Kataria, D.K. Gupta, P. Sahni, et al., Gastrointestinal mucormycosis–an uncommon isolated mucormycosis, Indian J. Gastroenterol. 17 (1998) 131–133.
[2] M. Rodden, T. Zaoutis, W. Buchanan, T. Knudsen, T. Sarkisova, R. Schaufele, et al., Epidemiology and outcome of zygomycosis: a review of 929 reported cases, Clin. Infect. Dis.: Off. Pub. Infect. Dis. Soc. Am. 41 (2005) 634–653.
[3] R. Gupta, S.V. Parelkar, S. Oak, B. Sanghvi, A. Prakash, Neonatal lingual and gastrointestinal mucormycosis in a case of low ano-rectal malformation-a rare presentation, J. Pediatr. Surg. 46 (2011) 745–748.
[4] E. Abedi, A. Sismanis, K. Choi, P. Pastore, Twenty-five years 'experience treating cerebro-rhino-orbital mucormycosis, The Laryngoscope 94 (1984) 1060–1062.
[5] D.S. Hibbett, M. Binder, J.F. Bischoff, M. Blackwell, P.F. Cannon, O.E. Eriksson, et al., A higher-level phylogenetic classification of fungi, Mycol. Res. 11 (2007) 509–547.
[6] S.A. Marques, R.M.P. Camargo, L.P.F. Abbade, M.E.A. Marques, Mucormicose: infecção oportunística grave em paciente imunossuprimido, Relat. cas. Diagn. Tratamento. 15 (2010) 64–68.
[7] P. Agrawal, U. Saikia, S. Ramanaathan, R. Samujh, Neonatal small intestinal zygomycosis misdiagnosed as intussusception in a two day old child with a review of the literature, Fetal Pediatr. Pathol. 32 (2013) 418–421.
[8] R.Y. Chinn, R.D. Diamond, Generation of chemotactic factors by Rhizopus oryzae in the presence and absence of serum: relationship to hyphal damage mediated by human neutrophils and effects of hyperglycemia and ketoacidosis, Infect. Immun. 38 (1982) 1123–1129.
[9] H.L.P. Orlowski, S. McWilliams, V.M. Mellnick, S. Bhalla, M.G. Lubner, P. Pickhardt, C.O. Menias, Imaging spectrum of invasive fungal and fungal-like infections, RadioGraphics 37 (2017) 1119–1134.
[10] H.E. Jensen, J. Salonen, T.O. Ekfors, The use of immunohistochemistry to improve sensitivity and specificity in the diagnosis of systemic mycoses in patients with haematological malignancies, J. Pathol. 181 (1) (1997) 100–105.
[11] M. Martinello, A. Nelson, L. Bignold, D. Shaw, We are what we eat! Invasive intestinal mucormycosis: a case report and review of the literature, Med. Mycol. Case Rep. 1 (2012) 52–55.
[12] S. Bonin, F. Petrera, B. Niccolini, G. Stanta, PCR analysis in archival postmortem tissue, Mol. Pathol. 56 (2003) 184–186.
[13] B. Spellberg, Gastrointestinal MM: an evolving disease, Gastroenterol. Hepatol. 8 (2012) 140–142.
[14] N. Guevara, D. Roy, C. Dutruc-Rosset, J. Santini, P. Hofman, L. Castillo, Mucormycosis–early diagnosis and treatment, Rev. Laryngol. Otol. Rhinol. 125 (2004) 127–131.
[15] Z.U. Khan, S. Ahmad, A. Brazda, R. Chandy, Mucor circinelloides as a cause of invasive maxillofacial zygomycosis: an emerging dimorphic pathogen with reduced susceptibility to pasoconazole, J. Clin. Microbiol. 47 (2009) 1244–1248.