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Mucor irregularis Infection and Lethal Midline Granuloma: A Case Report and Review of Published Literature

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Abstract *Mucor irregularis* (*Rhizomucor variabilis*) infection and lethal midline granuloma (LMG) are characterized by progressive swelling, ulceration, and destruction of the central face that is usually fatal. Pathological features are inflammation, necrosis, and granulation. LMG has been called by various names, and in recent years, it has been known as NK/T cell lymphoma. However, diagnosis still relies on the progressive necrosis course rather than malignancy in histology. The disease has long challenged physicians, particularly when it worsens with radiotherapy or chemotherapy but sometimes achieves total remission without anti-malignancy therapies. We describe a 35-year-old man who had typical clinical–pathological symptoms of LMG, which turned out to be primary *M. irregularis* infection; that was diagnosed by positive tissue culture and fungal elements in histology. The patient was successfully treated with antifungal therapy (liposomal amphotericin B, total 4,600 mg and amphotericin B total 277 mg, over a duration of 70 days). We hereby review current knowledge about the epidemiology, clinical manifestations, radiographic characteristics, and pathologic features of LMG with those of *M. irregularis* infection and their associations. We conclude that primary *M. irregulars* infection can mimic the clinico–pathological symptoms of LMG and the condition responds favorably to aggressive antifungal therapy.

Keywords Lethal midline granuloma · NK/T cell lymphoma · Mycosis · Mucorales · *Rhizomucor variabilis* · *Mucor irregularis*

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Introduction

Lethal midline granuloma (LMG) is a clinical–pathological syndrome characterized by progressive swelling, ulceration, destruction of the central face, and palate perforation, with pathologic features of inflammation, necrosis, and granulomation. The disorder was first described as "malignant granuloma" by Mcbride in 1897. Since then, a variety of names have been used such as "malignant granuloma," "nonhealing granuloma," "granuloma gangraenescens," "idiopathic midline destructive disease (IMDD)," and "lethal midline granuloma," all of which are descriptive names with unknown etiologic factors [1]. In histology, the disease is mainly described as the following entities: Wegener's type—granuloma with giant cell infiltration; Stewart's type—granuloma with

pleomorphic cell infiltration; [1, 2] and Tsokos's type—nonspecific inflammatory necrosis without granulomas and malignant cells [3].

With advances in immunohistochemistry, the disease was renamed "extra nodule NK/T cell lymphoma, nasal type" because the pleomorphic cells in the disease hold the T cell or natural killer cell marker, sometimes with atypical cells. However, diagnosis is still based on the aggressive necrosis course and immunohistochemistry [4] rather than the malignancy; the etiology remains unknown [5, 6]. Consequently, the diagnostic and subsequent therapeutic issues in the management of the disease have been challenging because the disease usually worsens with radiotherapy or/and chemotherapy [7] or recurs later on [8], although sometimes total remission is achieved without anti-malignancy therapies [9, 10].

Mucor irregularis (*Rhizomucor variabilis*) infection is a newly described disease that is characterized by symptoms of progressive central face swelling, ulceration, palate perforation, and midline face destruction with pathological features of inflammation, necrosis, and granulomation, quite similar to the characteristics of LMG. Is there any association between the two diseases? We present a case that meets both the criteria of LMG and *M. irregularis* infection.

Case Presentation

In March 2009, a 35-year-old Chinese man presented at the Third Hospital of Peking University with a 2-year history of progressive middle face swelling, ulceration, and midface destruction. The disease was traced back to 2 years previously when he manifested symptoms of nasal obstruction, discharge, lacrimation dacryorrhea, and later on with rhinorrhea and epistaxis. One year later, a red nodule appeared on his nasal root that progressively enlarged, and soon the entire external nose became swollen, and a perforation developed on his hard palate. He was suspected as suffering from LMG by the otorhinolaryngologists, stomatologists, ophthalmologists, and dermatologists he consulted. However, diagnosis had not been confirmed though he underwent multiple skin biopsies. In December 2008, his nose, lips, eyelids, and the central face became highly swollen and began to necrose. He was admitted to a hospital in south China, where he was treated with steroids, antibiotics, and antifungal therapy (itraconazole, 0.2 g per day) for a month. However, necrosis fulminated to the entire nose, lips, checks, eyelids, forehead, and the nasal bone, which lead to complete destruction of his face. He had lost his eyesight and olfaction 2 months previously, and he had lost 20 kg in body weight since onset. He denied a history of diabetes or immune disorders.

On admission, the patient had normal temperature, pulse, respiration, and blood pressure. His body weight was 41 kg. He could not see or smell because of swollen eyelids and defect of nose. His face was highly swollen, with widespread necrosis and defects of external nose, soft and hard palates, upper lip, and part of the lower lip. Eschars covered the necrotic area. The edges of the nasal and maxilla bone and the upper roots of teeth and gum were exposed (Fig. 1).

Blood tests showed hemoglobin 93 g/L, white cells 9.4×10^9 per cubic millimeter with 80.3 % band cells, 649×10^9 platelets/L, CD3 T cells 71.3 %, CD4 T cells 47.2 %, CD8 T cells 21.6 %, CD4 +/CD8 + ratio 2.19 (NR 0.9-2.0). Erythrocyte sedimentation rate was 83 mm/h. C-reactive protein 69.38 mg/L (NR < 1), normal blood glucose level, normal liver enzyme levels, normal renal function, low iron level (2.8 μmol/L), and total iron binding capacity (37.8 μmol/L), transferrin 147 mg/dL, prothrombin time 13.3 s, fibrinogen 4.85 g/L, globulin 42.2 g/L, and A/G 0.8, CH50 58 (NR23-46), IgG 21.4 g/L, IgE 2,500 IU/mL, Epstein-Barr virus-negative, HIV antibody–negative.

Computerized Tomography (CT, 2 months before presentation) showed signs of sinusitis of opacity, thickened membrane, and soft tissue enhancement of the face. Biopsies were performed in four regions, both on the necrotic areas and on the inflamed edge. Tissues were inoculated on SDA and cultured at both 25 and 37 °C. Three strains of light yellow filamentous fungus were recovered from tissues in the edges that were subsequently identified as *M. irregularis* with morphology (Fig. 2). With sequence analysis, the ITS area showed 99 % similarity to that of the type culture of *M. irregularis*, CBS 103.93.

Pathologic features were inflammation, necrosis, and granulation, as well as fungal invasion that varied in different areas. In the erythematous skin, histology featured with inclusive vasculitis with thromboses. Giant cells and multinucleated giant cells infiltrated the artery walls, forming thromboses, "onionskin" lesions, and artery destruction. Broad, predominantly aseptate and occasional pauciseptate, thin-walled hyphae could be seen in tissues, multinucleated giant

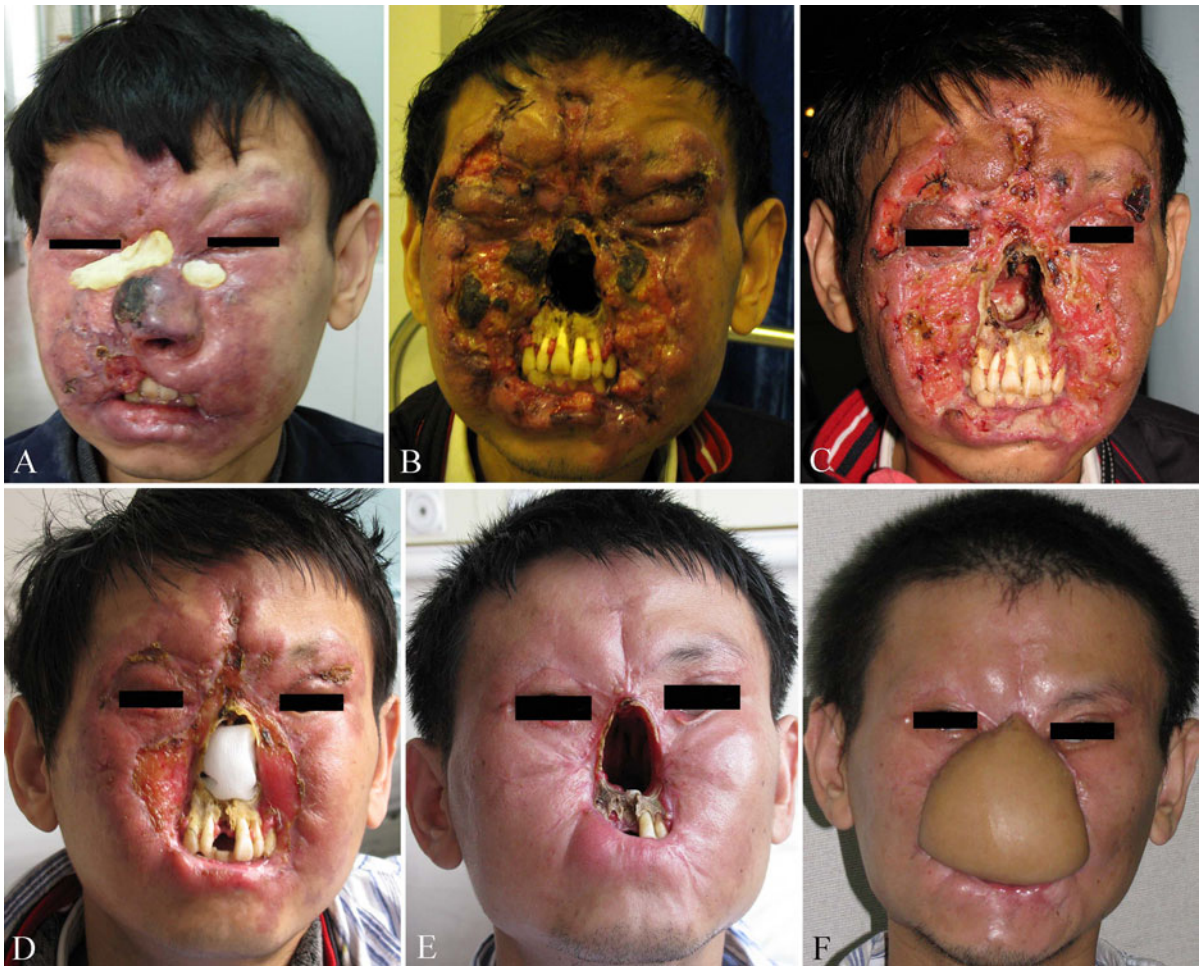

Fig. 1 Central face destruction and healing courses. **a** Highly swollen face with necrosis on the *right* nose wing and *upper lip*. **b** Widespread necrosis and defects of external nose, soft and hard palates, *upper lip*, and part of the *lower lip*. Eschars covered the necrotic area. The edges of the nasal and maxilla bone and the upper roots of teeth and gum were exposed. **c** Rapid improvement with antifungal therapy for a week. **d** Two weeks with antifungal therapy. **e** Two months with antifungal therapy. **f** With skin transplantation to reconstruct his nose and *upper lip*

cells, and artery walls and lumens, characterized by angioinvasion and angiocentric and angiodestructive lesions (Fig. 3). Tissues in necrotic area in the heartland featured predominately with granulation and infiltration of giant cells, plasmacytes, eosinophils and neutrophilic granulocytes, multinucleated cells, and a few atypical lymphoid cells, which were positive for CD3ε and CD56 and negative for CD20 and CD8 with in situ hybridizing method. The proliferation index (Ki67) of the lymphoid cells was 20–50 % in the nasal mucosa biopsy. EBV RNA was not detected.

The patient was diagnosed with *M. irregularis* infection and was managed immediately with antifungal therapy (liposomal amphotericin B and terbinafine), immunologic enhancement (thymopeptides), and antibiotics for accompanying infections. Liposomal amphotericin B (Lip AmB) was initiated at 25 mg/day and was increased to 100 mg/day within a week (25, 25, 50, 50, 75, 75, 100 mg/day, respectively). The dose of terbinafine was 0.25 g twice daily and subsequently once daily for 2 months. Thymopeptides were given intravenously at a dose of 1 mg daily for a month and gamma globulin at 5 g per day for 3 weeks.

Rapid improvement was observed right after treatment was begun. The second day, swelling began to lessen, and the patient could open his left eye. On the fourth day, he could open both his eyes and see clearly.

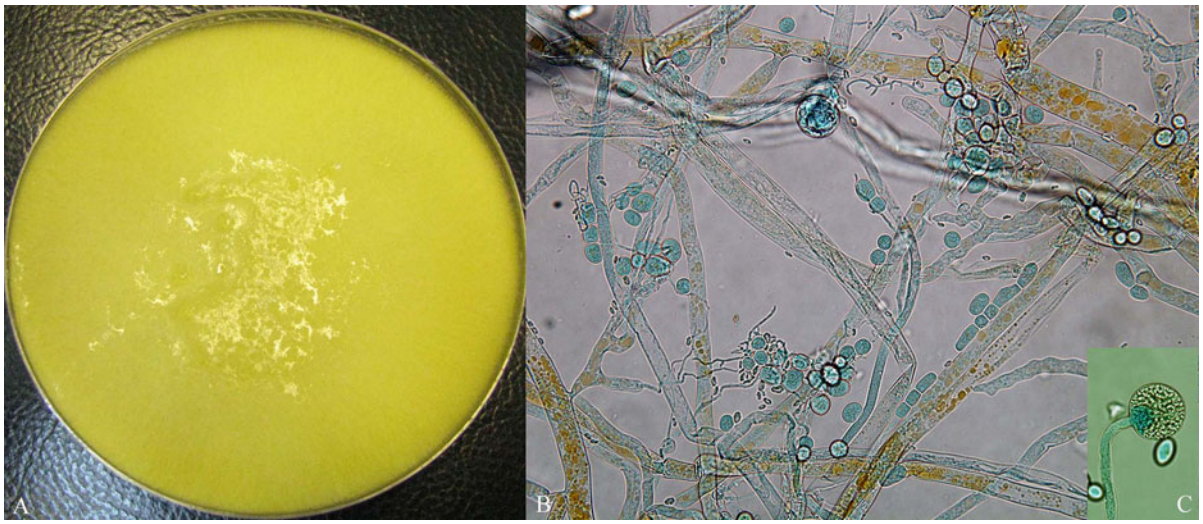

Fig. 2 The fungus recovered from biopsy tissue. **a** Lanose appearance with *yellow color* (10 days growth on PDA). **b**, **c** Thin-walled hyphae, rhizoids, chlamydospores, sporangiophores and sporangia (stained with lactophenol cotton blue, ×400)

A month later, necrotic areas were almost healed but with scarring. As lower eyelid ectropion and crostomia developed, he was transferred to a burn and plastic surgery hospital for skin transplantation, where he was treated with amphotericin B (25 mg/d) instead of Lip AmB because of financial problems. A week later, he experienced severe side effects of acute renal failure with blood urea nitrogen 14.78 mmol/L (NR 2.9–7.5) and creatinine 305 μmol/L (NR 53–130) and hypokalemia that recovered completely after discontinuing amphotericin B. However, the hospital did not transplant skin for him because there the patient was diagnosed with LMG again, so he was treated as an outpatient with Lip AmB and terbinefine for another month. The destructive area was completely healed with scarring, among which, the atypical cells disappeared with biopsy again. Half a year later, he was successfully transplanted with thick skin graft from his thigh to reconstruct his nose and upper lip (Fig. 1). On follow–up, a year after transplantation, the rebuilt nose was growing well and he had returned to normal life.

Review and Discussion

The case was characterized by (a) nasal airway obstruction with associated rhinorrhea and epistaxis; (b) palate perforation; (c) facial swelling and progressive midline destruction; (d) inflammatory vasculitis with angiocentric, angioinvasive, and angiodestructive characteristics; (e) giant cell granuloma; (f) a few atypical lymph cells positive for CD3ε and CD56; (g) broad, predominantly aseptate thin-walled hyphae in histology; (h) *M. irregularis* repeatedly isolated from tissue samples; (i) fast response to antifungal therapy and complete remission in the end. With (a)–(f), the patient met the criteria for LMG, and he fully met the criteria for primary *Rhizomucor* infection with (a)–(i). So the diagnosis would be LMG due to *M. irregularis* infection.

LMG is a life-threatening clinico–pathological entity characterized by swelling, ulceration, necrosis, perforation, granulation, and destruction of the central face, and *M. irregularis* infection is a crucial fungal disease that most commonly involves the central face with symptoms of sinusitis, followed by swelling, ulcers, and nasal septum and/or palate perforations [11–17].

Our patient met both the diagnostic criteria of LMG and *M. irregularis* infection and achieved complete remission with antifungal therapy. We review the epidemiology, risk factors, and radiology, and in particular, the clinical and pathologic features of LMG, comparing those of *M. irregularis* infection with those of other infections.

Epidemiology and Risk Factors

LMG is more often seen in Japan, China, Korea, Thailand, other Southeast Asian countries, Central and

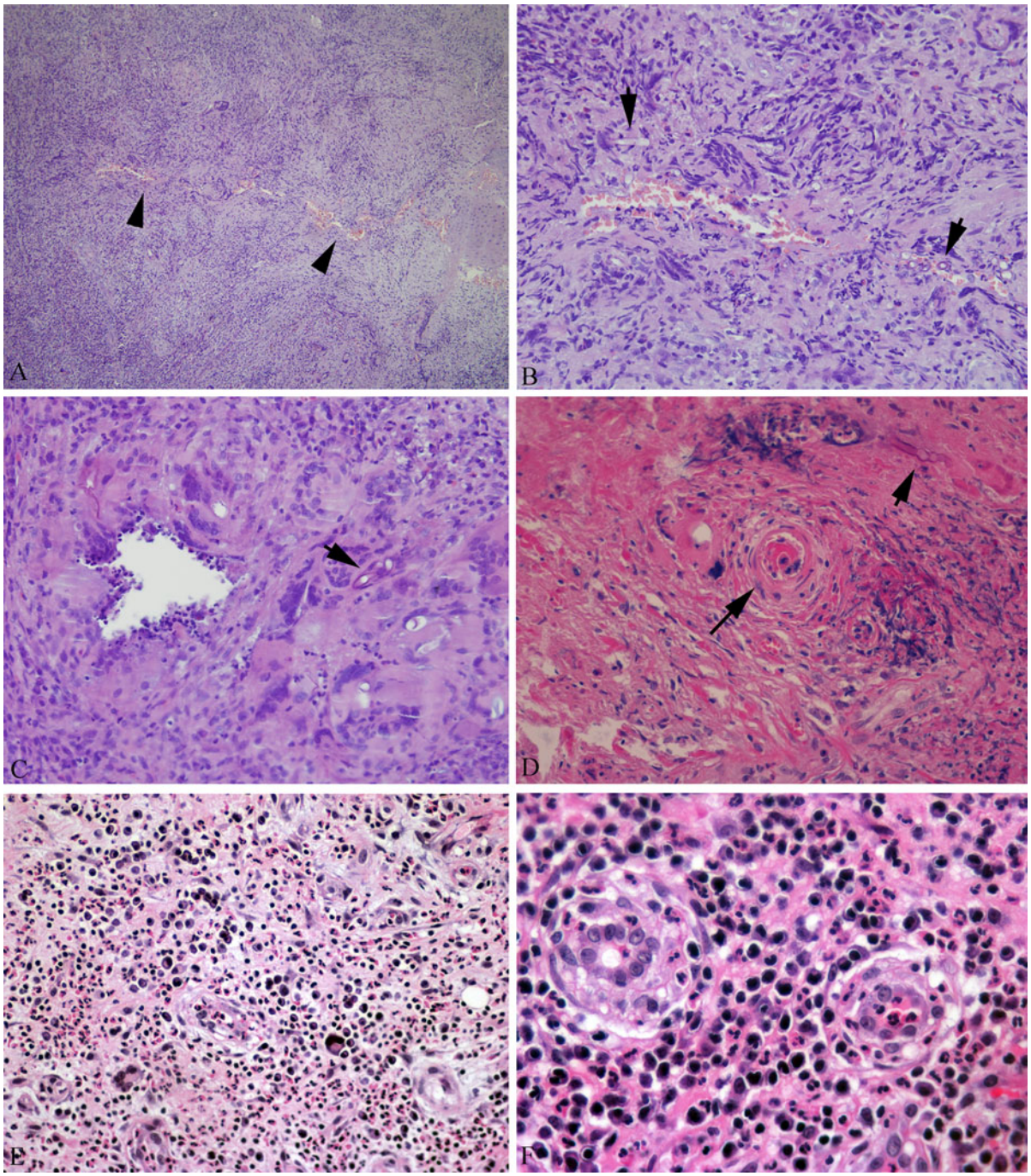

Fig. 3 Histological characteristics of inflammation, necrosis, and granulation, with fungal invasion that varied in different areas (stained with H&E). (No *tail arrows* mark the destructed artery, *short arrows* mark fungal hyphae or spores, and *long arrow marks* "onionskin" lesion.) **a** Granuloma with angiocentric and angiodestructive lesions (×40). **b** Fungal angioinvasion and giant cell infiltration (×400). **c** Inclusive vasculitis with infiltration of giant cells and multinucleated giant cells, within which, fungal hyphae and spores could be seen (×400). **d** "Onionskin" lesions and coagulative necrosis (×400). **e** Multicells infiltration with atypical cells (×400). **f** Atypical cells antioinvasion (×1,000)

South America, and other developing countries; it is rarely seen in the United States, Europe, and Australia [4, 18, 19]. In recent years, the number of patients diagnosed with LMG has increased greatly in China [20, 21].

Mucor irregularis is a fungus in the order Mucorales [22, 23], and *M. irregularis* infection is a newly recognized fungal disease mainly described in China that mostly involves the central face with symptoms of face swelling, ulceration, and nasal septum and/or palate perforations, commonly with a precursor of sinusitis [14, 17]. In pathology, the disorder features with giant cell vasculitis, necrosis, and pleomorphic cell infiltration with giant cells, multinucleated cells, plasmacytes, eosinophils and neutrophilic granulocytes, in addition to fungal elements [13, 15]. Ten patients, including the present one have been confirmed with the infection in China [11, 13–15, 23–27]. Eight of them involved the central face and most developed central face destruction [11, 13–15, 23–25, 28] and six with palate perforations [11, 13, 14, 25, 28]. Outside China, two patients with the disorder involving the central face or the palate were reported, one in US, and another India [12, 29], another two involving the skin was reported in Japan and Australia [30, 31].

Risk factors for LMG include association with immune disorders [32, 43], AIDS [32–35], staphylococcal infection [36, 37], drug use [38–42], steroid use [9, 43], and diabetes and other chronic illness [16, 44], all of which are consistent with risk factors for other infections, such as rhino-orbital-cerebral mycosis (ROCM) [16, 45], to which most of these *Mucor* cases would belong [12–15, 17].

Clinical Features

LMG is characterized by progressive inflammation and necrosis of the face and upper airways with symptoms of swelling, plaque, ulceration, perforation, destruction of the central face, and tissue defection [4, 19]. The disease usually begins as sinusitis, rhinitis, rhinorrhoea with symptoms of nasal congestion, discharge, epistaxis, nasal pain, and occasionally with loss of sense [8, 38, 47–52]. As it progresses, it often spreads to adjacent areas with subsequent symptoms [53–55].

Palate perforation is a direct result as the disease progresses that may be attributed to the fact the palate is the bottom wall of the maxillary sinus [39, 41, 56–60]. Through the perforation on the palate, yellow mucus or a necrotic mass can be seen within the maxilla above the palate [61]. Other structures of the sinuses, nasal turbinate, or the nasal septum can also be necrosed and perforated [53, 4, 19, 38, 39, 41]. Perforations may appear suddenly, as symptoms such as swelling and ulcer may be neglected at beginning [53, 4, 38, 39, 44, 57, 59, 61]. Occasionally, tonsils or the larynx may be involved, with symptoms of sore throat, indurate swelling, and ulceration [39, 54, 55, 59, 62].

Subcutaneous nodule, plaque, swelling, ulceration, and defects are also direct results of the disease spreading to the skin from the sinuses, or they may develop initially, or from traumas [1, 4, 6, 8, 38–42, 47, 49, 50, 52, 59, 61, 63–67]. Sequential symptoms of inflamed skin involving the nose and the central face tissue are characteristics of the disease, which is the reason for the names LMG and IMDD [6, 8, 19, 38, 40, 56–58, 61, 66, 68, 69]. Additionally, skin lesions usually feature as annual extending, a characteristic spreading manner of fungal or other infections [56, 61]. They may also manifest as cellulitis [51, 70]. Usually, ulceration or tissue necrosis develops on one side, first on the nose wing or lip [9, 60, 64, 69], which may be attributed to the fact that the supplying arteries are terminal in these areas [71]. Gingival involvement may develop, with subsequent bone destruction and tooth exfoliation [19, 57].

Orbital involvement may follow sinusitis or mouth or skin lesions because of direct diffusion or as a consequence of cavernous sinus involvement [8, 19, 43, 44, 48, 51, 52, 58, 67, 72, 73]. Common signs of orbital involvement are the results of focal neurological deficits such as ptosis, proptosis, diplopia, ophthalmoplegia, facial paralysis, and vision loss [34, 44, 48, 52, 67]. Occasionally, uveitis and vitritis can develop [52, 67]. These symptoms may occur without sinusitis if the disease initiates at the eye or orbit [51, 67]. Soft tissue inflammation, of the eyelids and periocular erythema, swelling, and ulceration are common signs of orbital involvement, or they may be the direct results of skin involvement [19, 43, 36, 51].

Systemic symptoms such as fever, malaise, and weight loss may be present at late stages [4]. White blood cells, blood sedimentation, and C-reactive protein may be elevated [54]. If the pituitary is involved, hypopituitarism may occur [44]. If the lung, brain, gastrointestinal tract, bone marrow, kidney, or

lymph glands are involved in the disease, relevant symptoms would follow [34, 74]. If the infection disseminates via blood to the skin, dark purple nodules or firm, infiltrative plaques may emerge [50, 75]. At end stage, hemophagocytic syndrome, secondary infection, or multiorgan failure may develop [36, 54, 65, 74, 76].

Mucor irregularis infection and other fungal infections in the central face manifest with the same symptoms of sinusitis, indurate swelling, ulcer, perforation, and destruction (Fig. 4) as LMG does. [13, 14, 17, 29, 43, 52, 58, 73, 78, 79]. They cannot be differentiated by clinical features. Most of the above symptoms were seen in our patient, who was repeatedly suspected as having a neoplasm before he came to us.

Image Characteristics

Extensive soft tissue mass or enhancement can be seen with radiographs, CT, or MRI [73, 58, 72, 81, 82]. Mostly, signs of sinusitis such as fluid density, air–fluid level, mass image, sinus expansion, nasal passage blockage, and diffuse mucosal thickening can be seen in the maxilla, ethmoid, sphenoid, and frontal sinuses [43, 47, 51, 54, 58, 72, 80, 83]. More than 50 % of cases show involvements of the adjacent alveolar bone, hard palate, orbits, and nasopharynx [58, 43]. However, bone erosion or destruction is suggestive but not diagnostic of the disease [58, 81]. Orbit involvement is sometimes seen with proptosis or enhanced mass in the cavernous sinus [8, 43, 44, 48, 51, 52, 72, 73, 80, 83]. Most of the above characteristics except the orbital signs were seen in the present case, and all of them could be signs of ROCM [16].

Pathologic Characteristics

Inflammation, necrosis, and granulation are main features of LMG, a pattern of inflammatory reaction accompanied with giant cell vasculitis [3, 6, 61].

Inflammation is usually nonspecific [3, 8, 9, 43, 48, 57], acute or chronic [3, 6], involving predominantly giant cells, lymphocytes, plasma cells, and sometimes multinucleated macrophages [3, 4, 8, 9, 33, 39, 42, 43, 54, 57, 60, 67, 69].

Ischemic necrosis is characteristic of LMG following inclusive vasculitis with thrombosis, artery wall necrosis, and giant cell infiltration [1, 3, 39, 42] that gives rise to the describing terms of angioinvasive, angiocentric, and angiodestructive [33, 43, 47, 48, 50–52, 67, 70, 84]. "Onionskin" lesions can be seen if giant cells infiltrate to the artery wall [1, 43].

Granulation, a compensation response secondary to necrosis, is another feature of LMG, involving predominantly giant cells (with or without multinucleated giant cells) mixed with lymphocytes, plasma cells, and multinucleated macrophages [1, 43, 48, 51, 61, 67, 85].

All of the above features are signs of infection and were seen in the present patient and the patients with *M. irregularis* and other fungal infection [13–15, 23, 27–29, 46, 77, 78].

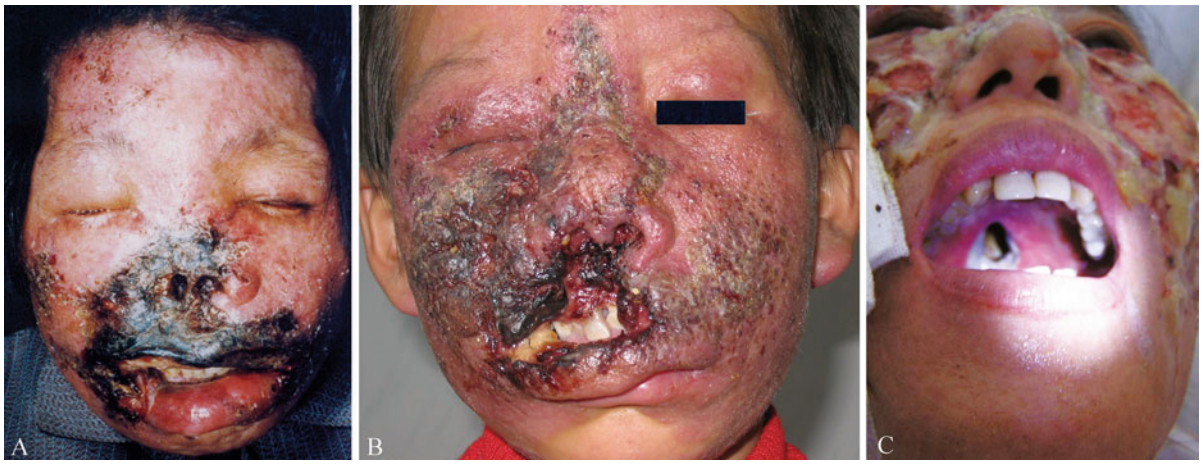

Fig. 4 Central face swelling, ulceration, destruction, and palate perforation due to *M. irregularis* infection and other fungal infections (**a** from Dr. Ai-Ping Wang and Ruo-Yu Li [28]; **b**, **c**, from Dr. Wei-Da Liu [13, 14]. Copyrights permitted)

Among the infiltrating cells, there may exist some atypical cells [43, 54], which are positive for CD56 expression and cytoplasmic CD3ε with negative surface CD3 in inmmunohistochemistry, which may need repeated or multiple biopsies [69]. Biopsy can be positive with Epstein-Barr virus in tissue [86]. Epstein-Barr virus-negative cases have been reported [87].

In the present case, atypical cells needed to diagnose LMG were detected in one of the biopsy regions, which were the necrotic center of the left check, with granulation, but these cells disappeared completely after antifungal therapy.

Associations of LMG with *M. irregularis* and Other Infections

Epidemiologic, clinical, radiologic, and pathologic characteristics of the newly described *M. irregularis* infection are similar to those of LMG, which has confused physicians for more than a century depending on histology and has been historically diagnosed according to characteristics of progressive ulceration, inflammation, ischemic necrosis, and granulation, all of which are typical signs of infection [16, 28, 88]. In addition, repeated or multiple biopsies and immunohistochemistry are usually needed because the atypical cells are difficult to trace [55]. The present case met both the criteria for *M. irregularis* infection and LMG, and because the atypical cells disappeared after antifungal therapy, we could not deny the close relationship between *M. irregularis* infection and LMG; a disease with poor survival rate even when patients received radiochemotherapy and chemotherapy [19, 21, 61, 89, 91]. Some investigators have speculated that less toxic treatment regimens would be of advantage in such cases [62]. Moreover, LMG has been associated with actinomycetes and bacterial infections. In 1996, van Putten reported patients of Wegener's granulomatosis associated with *Staphyloccus aureus* infection [37]. Their clinical manifestations and c-ANCA tilters fluctuated in accordance with severity of lower respiratory tract infections with *S aureus*, but they declined after sulfamethoxazole/trimethoprim therapy, to which the pathogen was sensitive [37]. In animals, an LMG-like case with *Nocardia* infection was confirmed by pathology [92]. Other cases, however, regressed without therapy [92] or with only antidiabetic therapy for the original disease [9]. One patient died after chemotherapy, and the infection was shown to be Mucorales on a postmortem nasal cavity biopsy [88]. In 2005, Zhang et al. reported a 16-year-old Chinese male patient whose nose was destroyed within 3 months. He was diagnosed as NK/T cell lymphoma and died after receiving radiochemotherapy and chemotherapy. Fungal elements were detected in histology and with direct KOH examination that was confirmed as *Fusarium solani* cultured from the necrotic tissue sample [91].

It is difficult to demonstrate fungal elements in tissue [93] or culture them [92]. The broad, thin-walled hyphae are easily broken down in tissue with decreased nutrition or are attacked by macrophage cells or NK/T cells (Fig. 3). *M. irregularis* could not be recognized but could be transferred from the infected tissue to the animal model [93] in the same way that NK/T cell lymphoma can be copied in mice by transplanting lesion tissue to the animal [94]. In our patient, it was difficult to recognize the fungal elements or culture the fungus from tissues in granulomatous areas, where tissue cultures were repeatedly performed before he came to us.

Conclusions

Both *M. irregularis* infection in the central face and LMG are characterized by erythematous swelling, progressive necrosis, perforations and destruction, commonly with a precursor of sinusitis. In pathology, they feature with inflammation and giant cell vasculitis and their consequences of coagulative necrosis and granulation. Because the two diseases converged in our patient, and because of other evidence of infections with LMG, although data are limited, we consider that *M. irregularis* is probably one of the etiological agents of LMG.

Search Strategy and Selection Criteria

We searched Medline for English and Chinese language manuscripts limited to "human" and "case reports," "letters," "reviews," and "clinical conferences" from 1966 to 2012. We used MeSH terms "granuloma, lethal midline," or "Wegener's granulomatosis," "extranodal NK/T cell lymphoma" in combination with MeSH term "nose" for lethal midline granuloma. We also used the terms of "Rhizomucor [MULTI]" OR "*Mucor irregularis*" in

combination with terms of "nose" [MeSH Terms] or "face"[MeSH Terms] or Palate[MULTI] or "pharynx" [MeSH Terms] for *M. irregularis* infections in the central face.

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Conflict of interest None.

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