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內文：

Abstract

- Invasive fungal sinusitis is a life-threatening infection in immunocompromised patients.
- Its onset is rapid and leads to severe complications.

Introduction

- Invasive and systemic fungal infections are becoming major causes of morbidity and mortality among immunocompromised patients.
- Despite prophylactic and empirical antifungal treatment, the emergence of breakthrough invasive fungal infections caused by theoretically sensitive organisms as well as resistant organisms has raised serious concern in immunocompromised patients, who show a poor prognosis
- Invasive fungal sinusitis has increasingly been recognized as a life-threatening fungal infection in patients with hematological malignancies
- Aspergillus species account for most cases of invasive fungal sinusitis

Table 1
Summary of data for previously reported cases of ISA.

Reference (number of cases)	Signs and symptoms	Serological examinations	X-ray examination	Biopsy	Anti-fungal treatments Surgical treatments
7 (5)	Nasal congestion Facial swelling Sinus pain Nasal necrosis	Negative *Aspergillus* galactomannan antigen	Positive findings including CT and MRI	Positive histology Positive culture	VRCZ and AMPH-B Surgery and drainage
8 (3)	Nasal congestion Nasal discharge Eyelid edema Headache	N.D.	Positive findings including CT	Positive histology Positive culture	AMPH-B Surgery
9 (12)[a]	Nasal congestion Sinus pain Periorbital swelling Nose ulceration	N.D.	Positive findings including CT	Positive histology Positive culture	AMPH-B Surgery (9 of 12 cases)

Note: AMPH-B, amphotericin B; VORZ, voriconazole; N.D., not done.
[a] Twelve of 17 patients with invasive mold sinusitis developed ISA.

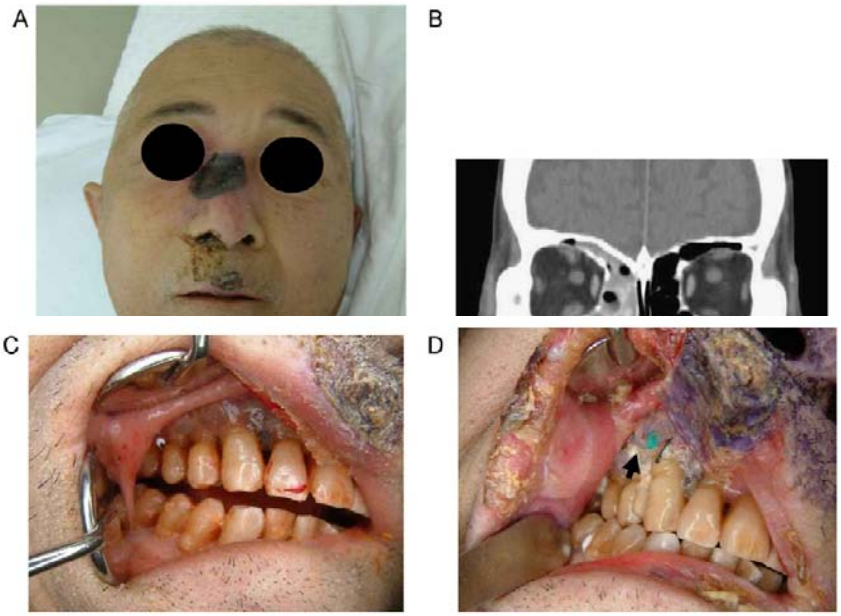
- The prognosis of patients with ISA depends on the underlying disease, the stage of infection, and anti-fungal management, with the fatality rate ranging from 28.6% to 88.1%
- Early diagnosis and aggressive therapy are critical to achieve optimal therapeutic results
- In general, the early signs and symptoms of ISA are subtle, and the disease must be distinguished from bacterial infection
- Serological tests for the detection of (1-3)-β-d-glucan and Aspergillus galactomannan antigen have been developed for the early diagnosis of invasive

aspergillosis

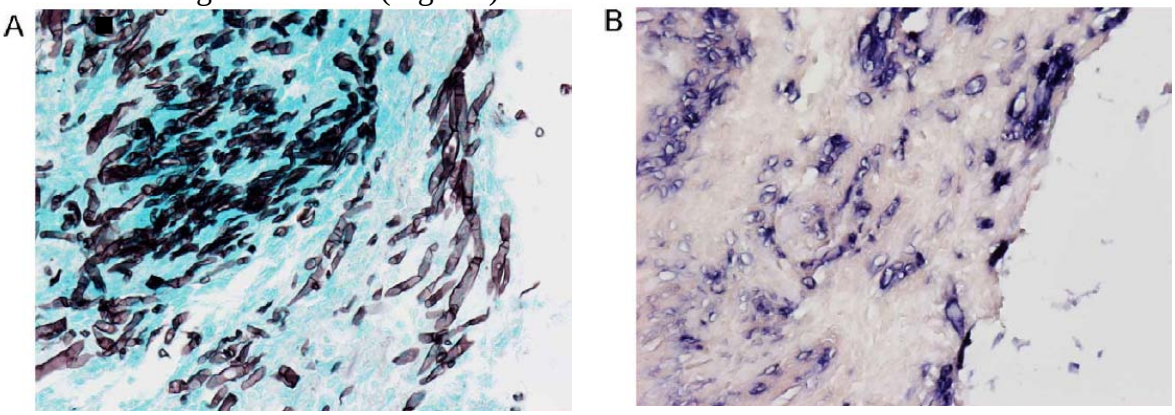
- A preliminary molecular diagnostic method based on in situ hybridization in tissue sections has been found to be more useful than culture-based diagnosis for the rapid and accurate diagnosis of invasive aspergillosis
- Treatment should include resection of the infected tissue in conjunction with intensive treatment with systemic antifungal agents
- Patients with ISA may not be curable when the infection is diagnosed at the advanced and late stages.

Case report

- A 69-year-old man with relapse of AML was admitted for reinduction chemotherapy (enocitabine, idarubicin, and etoposide).
- On day 13
  - The patient was placed on itraconazole (ITCZ; 200mgpo q.d.) for antifungal prophylaxis because of a dramatically decreased leukocyte count (100 cells/μl: 0% neutrophil).
- On day 23
  - The patient was febrile and unresponsive to antimicrobial treatment with panipenem and amikacin.
  - Due to persistent fever and marked neutropenia, empirical antifungal treatment of micafungin (MCFG; 150mg iv q.d.) was started combined with ITCZ.
- On day 29
  - The patient was referred to the Department of Dermatology because he complained of right nasal pain and facial erythema.
  - The skin lesion was biopsied and histopathological examination of HE-stained tissue sections demonstrated inclusion bodies in epidermal cells suggesting a viral infection of the skin.
  - The serum level of (1-3)-β-d-glucan was slightly elevated (12.8 pg/ml; normal value <11 pg/ml).
- On day 39
  - The patient was referred to the Department of Oral Surgery because a black necrotic crust rapidly developed at the right root of the nose and caused facial swelling; in addition, he complained of severe right buccal pain, nasal congestion, and nasal discharge (Fig. 1A).
  - CT scans demonstrated a destructive lesion in the maxillary sinus that invaded the ethmoidal sinus, but there was no intracranial involvement (Fig. 1B).
  - Oral examination demonstrated a wide destructive ulcer in the right maxillary mucogingiva, which was covered by a gray, necrotic pseudomembrane (Fig. 1C).
  - His serum had a high concentration of (1-3)-β-d-glucan (54.2 pg/ml) and was positive for Aspergillus galactomannan antigen (4.9 ng/ml; normal value <0.5 ng/ml), strongly suggesting ISA.
  - His leukocyte count was 200 cells/μl (10% neutrophils) and his platelet count was 22,000 cells/μl.



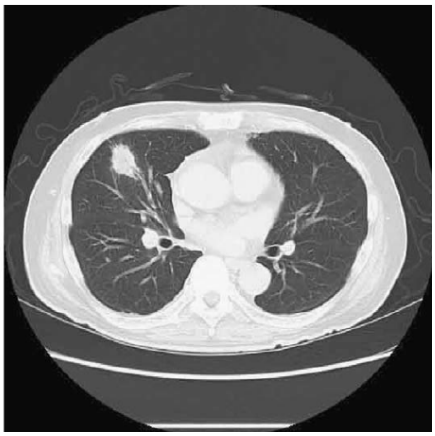
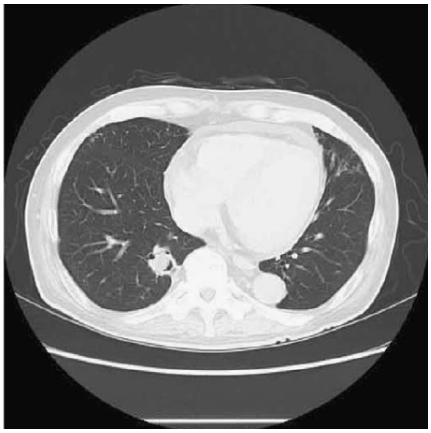
- On day 41
  - Antrotomy of the maxillary sinus and debridement of the necrotic gingiva were performed under local anesthesia with platelet infusion.
  - After the necrotic tissues were removed, a Penrose drain was placed for washing and instilling antifungal drugs into the surgical wound area (Fig. 1D).
  - Fungal hyphae were found in a 10% KOH preparation of the tissue sample, supporting the diagnosis of ISA.
  - Both MCFG and ITCZ were discontinued and the patient was started on voriconazole (VRCZ; 200mg po b.i.d.) combined with liposomal amphotericin B (l-AMPH-B; 150mgiv q.d.)
  - Sinus rinses with AMPH-B (1 mg/ml diluted in distilled water) once a day as part of his post-surgical care.
- On day 43
  - Histopathologically, Grocott-stained tissue sections showed organisms with dichotomously branched septate hyphae at acute angles, supporting the diagnosis of ISA (Fig. 2A).



- On day 45
  - The hyphae in tissue sections were identified as Aspergillus species by in situ hybridization using a highly specific DNA probe for Aspergillus species, thereby confirming the ISA (Fig. 2B).
- on day 53

- Tissue culture on Sabouraud's dextrose agar yielded fungi that were morphologically identified as A. fumigatus.

- On day 55
  - The patient was still febrile and complained of persistent cough. The level of (1-3)-β-d-glucan dramatically increased to 364.1 pg/ml, and the serum was positive for Aspergillus galactomannan antigen.
  - Thoracic high-resolution CT scans demonstrated several nodules (Fig. 3A) and a dense, cavitating infiltrate with halo sign in the lower lobes of both lungs (Fig. 3B), suggesting invasive pulmonary aspergillosis.

A  B 

- On day 65
  - The oro-facial necrotic area showed gradual improvement
  - No symptoms suggestive of intracranial invasion. In addition, the level of (1-3)-β-d-glucan decreased to 254.6 pg/ml.
  - After receiving human recombinant G-CSF (2400μg/total), the leukocyte count increased to 1000 cells/μl (43% neutrophils).
- on day 71
  - The patient with relapse of AML suddenly developed severe respiratory failure
- on day 79
  - His condition deteriorated and he died
  - An autopsy was not performed.
  - In vitro susceptibility testing showed that the causative A. fumigatus was sensitive to MCFG (MIC = 0.03125μg/ml), ITCZ (MIC = 0.25μg/ml), VRCZ (MIC = 0.125μg/ml), and AMPH-B (MIC = 0.25μg/ml).

Discussion

- Invasive fungal infection remains the most common infectious cause of death among neutropenic patients undergoing induction chemotherapy for AML
- Breakthrough invasive fungal infection including aspergillosis in patients receiving prophylactic or empirical treatment is a well-known problem and results in a high mortality rate
- In the present case, the patient developed ISA during prophylaxis with ITCZ and empirical therapy with MCFG, which have been shown to be effective against isolated A. fumigatus in vitro, suggesting the possibility that the plasma concentrations of these agents were ineffective for a patient with deep neutropenia
- ISA is characterized by rapid spread of the fungus from the sinus airspace into adjacent structures with a very high mortality rate
- Early diagnosis and aggressive treatment of ISA are essential for patient survival

- The reported symptoms of ISA include nasal congestion, nasal discharge, abnormal findings in the nasal cavity, buccal swelling with pain or numbness, gingival and skin necrosis, and high fever, but these symptoms are not always specific to ISA
- A definitive diagnosis requires histological and cultural confirmation based on surgical specimens
- Serological assay for (1-3)-β-d-glucan is highly sensitive for fungal infections but not specific for aspergillosis, while the detection of Aspergillus galactomannan antigen is less sensitive but more specific
- A high level of (1-3)-β-d-glucan and positive Aspergillus galactomannan antigen indicated Aspergillus infection.
- We performed in situ hybridization using an Aspergillus-specific DNA probe to confirm the diagnosis of aspergillosis.
- Although the method is still preliminary, in situ hybridization is a promising technique for a more prompt diagnosis compared to culture-based methods, which are often time-consuming and carry the risk of growth failure due to incorrect handling of the tissue samples.
- Aggressive systemic anti-fungal therapy is necessary to eradicate Aspergillus infection in immunocompromised patients.
- Amphotericin B was long the standard treatment for ISA, but the current standard therapy is VRCZ, which has led to better responses and improved survival to help pharmacological therapy reach the infected area, immediate surgical debridement of the necrotic tissue is necessary.
- Published case series strongly supports the need for surgical debridement plus antifungal agents to optimize the outcome, showing a 60% survival rate for patients with ISA that would otherwise be as low as 28.6%
- In conclusion, fungal infection should be clinically diagnosed at an early stage and treated with surgery in combination with intensive antifungal administration to significantly reduce the mortality rate in neutropenic patients with AML.

題號	**題目**
1	Aspergillosis 的臨床特徵何者為非? **(A)** 病灶切片可發現菌絲分支 **(B)** 血管有壞死的現象 **(C)** 免疫力正常的病人不會有組織壞死的現象 **(D)** 免疫力低下的病人常造成大範圍的組織破壞
答案(C)	出處： oral & maxillofacial pathology 2nd p207~p209
題號	**題目**
2	Aspergillosis 的預後與處理何者為非?
	(A) 手術移除是不必要的 **(B)** Itraconazole 或 amphotericin 投藥 **(C)** 免疫力低下的病人預後不佳 **(D)** Allergic fungal sinusitis 可投予類固醇
答案(A)	**出處：oral & maxillofacial pathology 2nd p207~p209**