症例 1

造血幹細胞移植後に発症した肺ムーコル症

虎の門病院　臨床感染症科
荒岡　秀樹

（症例）35 歳，男性
（基礎疾患）急性骨髄性白血病，臍帯血移植レシピエント
（既往歴・家族歴）特記すべきことなし
（生活歴）喫煙歴　20 本/日×15 年

（現病歴）
（X-1）年に急性骨髄性白血病（AML with MDS-related cytogenetic changes：複雑核型）と診断された．2 度の寛解導入療法を要し，寛解の状態でシクロホスファミド＋全身放射線照射 12Gy の前処置で骨髄移植を施行したが，移植後 87 日に再発した．その後，種々の化学療法抵抗性であり，寛解に至らなかった．経過中に肺炎を発症し，器質化肺炎の合併も疑われた．抗菌薬，抗真菌薬（ボリコナゾール，その後リポソーマル・アムホテリシン B），ステロイド投与で肺病変は改善し，X 年臍帯血移植施行目的に当院紹介となった．入院時の胸部 CT では肺野の所見は消失していた．

（移植計画）
前処置：フルダラビン 180mg/m^2，メルファラン 80mg/m^2，ブスルファン（静注）12.8mg/kg
GVHD 予防：タクロリムス
ドナー：臍帯血　総細胞数：2.80×10^7/kg
CD34：1.03×10^5/kg
HLA 適合　血清：GVH 4/6　HVG 4/6
アリル：GVH 4/6　HVG 4/6

（感染対策）
環境要因：個室の無菌室（クラス 100）
感染症スクリーニング検査：発熱時の血液培養，週 1 回の胸部 X 線，週 1 回の β-D- グルカン，週 1 回のアスペルギルス GM 抗原
予防薬：レボフロキサシン 500mg/日，アシクロビル 600mg/日，ボリコナゾール 500mg/日

（入院後経過）
器質化肺炎に対し投与していたプレドニゾロン 20mg/日は漸減し，移植当日で投与終了した．移植前日に 38 度台の発熱が出現し，血液培養 2 セット採取後セフェピムの投与を開始した．その後移植後 2 日から肛門痛が出現したため，血液培養 2 セット採取後メロペネムへ抗菌薬を変更した．血液培養は陰性であったが，移植後 5 日の時点で 39 度の発熱が持続していた．

（移植後 5 日の所見）
身体所見：体温 38.0℃　血圧 108/72mmHg　HR 113 回/分　呼吸数 18/分　SpO_2 98%（室内気）　右下肺野の呼吸音軽度低下　腹部：平坦　軟　圧痛なし　肛門：明らかな腫脹なし　皮疹認めず
検査所見：
WBC 10/μL，Hb 7.9g/dL，Plt 8,000/μL，T-Bil 0.4mg/dL，AST 12IU/L，ALT 11IU/L，ALP 233 IU/L，γGT 53IU/L，LDH 81IU/L，BUN 16mg/dL，Cre 0.5mg/dL，Na 140mmol/L，K 3.7mmol/L，Cl 106mmol/L，CRP 9.4mg/dL，Glu 99mg/dL，HbA1C（JDS）6.5%
β-D グルカン（Wako 法）＜6.0（pg/mL），アスペルギルス GM 抗原　＜0.1，クリプトコックス抗原（－），サイトメガロウイルス抗原（－）
ボリコナゾール　トラフ値：1.18mg/L（移植 6 日前），0.95mg/L（移植前日）
血液培養陰性　喀痰培養有意菌検出せず

（鑑別疾患）
発熱性好中球減少症の状態であり，通常感染巣がわかりづらいことも多いが，本症例では身体所見から呼吸器感染症であることが想定された．
細菌感染症としては，細菌性肺炎を第一に考え，肛門周囲炎も鑑別に入れた．また，真菌感染症としては，ボリコナゾール投与下に生じた肺真菌症，副鼻腔真菌症を鑑別疾患にあげた．

（その後の経過）

追加検査として，胸部 X 線，胸部 CT を施行した．移植後 5 日の胸部 CT（Fig. 1）において，右下葉に径 4cm 大の周囲にすりガラス陰影を伴う腫瘤陰影を認めた．移植前日と移植後 6 日（Fig. 2）に施行した胸部 X 線を比較すると，右下肺野に新たな結節陰影が出現していることがわかる．

原因微生物を特定するため，この時点で気管支鏡検査を実施した．気管支肺胞洗浄を施行し，細胞数少数，洗浄液のアスペルギルス GM 抗原は 0.3，グロコット染色は陰性，培養は陰性であった．併せて施行したウイルス PCR は Adenovirus 陰性，RS virus 陰性，Parainfluenza-3 のみ陽性であった．

この時点での鑑別疾患として，ボリコナゾール投与下に生じた肺真菌症を，また上記の検査結果もふまえてムーコル症を第一に考えた．よって，ボリコナゾールからリポソーマル・アムホテリシン B 10mg/kg/日（本邦における保険用量は 5mg/kg/日まで）とミカファンギン 150mg/日の併用療法へ変更した．

その後血球が生着し，治療および確定診断を目的として，移植後 119 日に胸腔鏡下肺切除術（VATS）を施行した．病理肉眼所見では，4cm 大の暗赤色結節に加え，周囲に境界不明瞭な黄色調領域を認めた．組織学的には出血性梗塞と周囲に広がる器質化肺炎を呈していた．梗塞巣の中に隔壁の乏しい糸状真菌が集簇し，強い血管侵襲性を呈していた．菌糸は PAS 染色陽性，グロコット染色陽性であった．培養は陰性であった．

詳細な解析目的に，国立感染症研究所での検査を依頼し，組織の PCR で *Cunninghamella bertholletiae* の遺伝子を検出した．薬剤感受性は不明であった．（国立感染症研究所　梅山隆先生，大野秀明先生，宮崎義継先生方との共同研究）

リポソーマル・アムホテリシン B を投与継続し，呼吸状態や全身状態も安定し，投与を終了した．リポソーマル・アムホテリシン B の総投与期間は 211 日，総投与量は 108,600mg であった．血清のクレアチニン値は治療開始前 0.6mg/dL，治療終了時には 1.3mg/dL であった．移植後 153 日の胸部 CT を Fig. 3 に提示する．軽快退院となっている．

（最終診断）*Cunninghamella bertholletiae* による肺ムーコル症

（症例の疑問点から研究的考察へ）

本症例では，発症早期から真菌感染症を疑い，気管支鏡を実施した．それにもかかわらず，確定診断には至らなかった．その後 VATS を施行し，その培養でも真菌は検出されず，PCR 法を用いて *Cunninghamella bertholletiae* の遺伝子を検出した．ムーコル症の診断の難しさに焦点をあて，下記の 3 つの疑問点をあげ議論をすることとした．

Fig. 1　移植後 5 日の胸部 CT

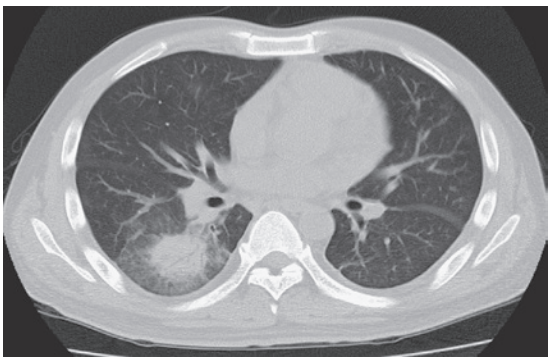


Fig. 2　移植前日（左）と移植後 6 日（右）の胸部 X 線

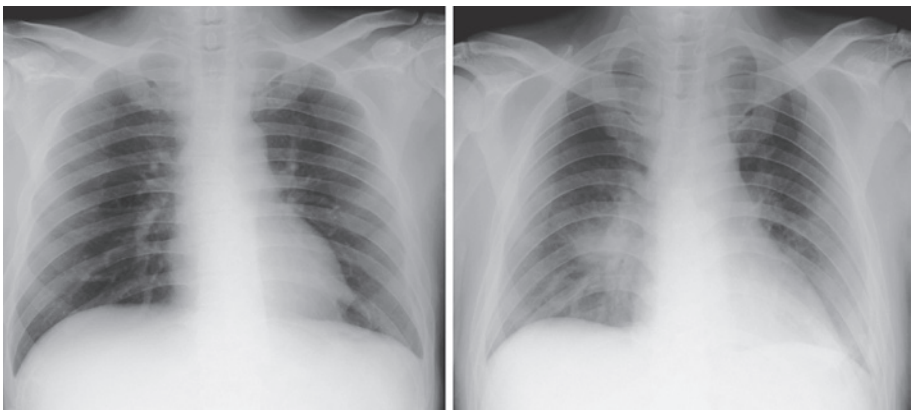
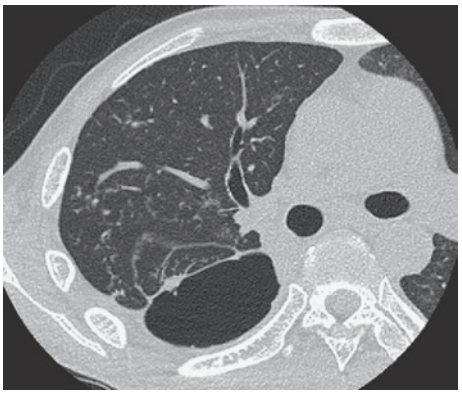


Fig. 3　移植後 153 日の胸部 CT



本症例（ムーコル症）の疑問点

1. ムーコル症の疫学は？

2. 診断法の有用性と今後の課題

3. 得られた検体を培養する場合，検出感度をあげるためにすべきことは？

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利益相反自己申告：申告すべきものなし

“本症例の疑問点”から“研究的考察”へ

[1]国立感染症研究所真菌部，[2]虎の門病院臨床感染症科

梅山　隆[1]　荒岡　秀樹[2]　大野　秀明[1]　田辺　公一[1]
山越　智[1]　名木　稔[1]　宮崎　義継[1]

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1. ムーコル症の疫学は？

ムーコル症は，これまで接合菌症が一般的な呼称として使われてきた．しかし，最近の分類法に基づいて，現在ではムーコル症として称されることとなった．自然界に多くの菌種のムーコルが広く分布しているが，ヒトの病原体としては一部の菌種である．主要な病原体は *Rhizopus oryzae* と *Rhizopus microsporus* とされている．*Mucor* 属と *Cunninghamella* 属は頻度が少ないが，臨床上重要である．その他，*Absidia* 属，*Rhizomucor* 属も検出される．

病変部位として，鼻脳，肺，消化管，皮膚が挙げられる．主要感染部位は基礎疾患によって大きく異なり，悪性腫瘍・骨髄移植の患者では肺ムーコル症が最も多く（それぞれ 60%, 52%），糖尿病患者では鼻脳型（43%），基礎疾患のない患者では皮膚ムーコル症が多い（50%）[1]．米国 TRANSNET（Transplant-Associated Infection Surveillance Network）による疫学解析では，発症率は低く，造血幹細胞移植 1 年で 0.29%，固形臓器移植 1 年で 0.07% である[2]．イタリアでの 1988 年から 1997 年の疫学調査によると，ムーコル症の死亡率は 73% で，アスペルギルス症（49%）と比較して高い[3]．

2. 診断法の有用性と今後の課題

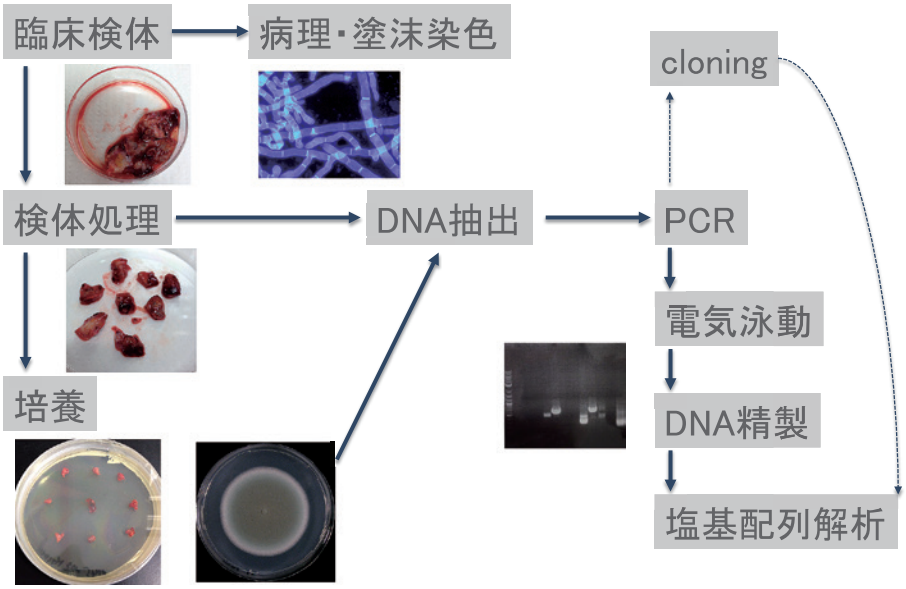
他の深在性真菌症と同様に，ムーコル症においても，治療の遅延が予後を大きく左右することが報告されている．診断が困難で，生前に診断が付く率は 25% 程度である[4]．血液培養が陽性になることはまずなく，臨床検体からの培養陽性率も非常に低い．特徴的な血清学的検査もない．アスペルギルス症とムーコル症とを臨床的に鑑別することは非常に難しいが各々の治療方針が異なるため，可能な限りの組織学的な考察が重要である．

真菌同定検査の流れを Fig. 1 に示す．真菌同定の基本はやはり培養である．しかしながら，培養陽性率は極めて低い．2002 年までにムーコル症として報告された 204 例のうち，菌が分離同定されたものは 14 例（6.9%）であった[5]．培養陽性率を上げるための工夫については次項の考察で述べる．培養陽性となれば，形態学的観察とともに遺伝子検査を行い，原因真菌を同定する．今回の症例では，臨床検体（パラフィン切片）から直接遺伝子検査を行うことにより，病理診断とともに *Cunninghamella bertholletiae* によるムーコル症と診断できた．

ムーコル症の病理診断は困難である．米国の調査で真菌培養陽性 338 例（1997～2007 年）のうち，病理診断と培養検査結果が異なった糸状菌症例が 8 例あり，そのうち 4 例がムーコル症に関する誤診であったことからも，その困難さが窺える[6]．それでも病理組織学的検査は，培養検査で検出された真菌が外界環境からの汚染なのか，組織侵襲性を持つ病原体なのかを区別でき，ムーコル属に特徴的な血管侵襲性の有無を確定できる唯一の診断法であり，きわめて重要な手段である．典型的なムーコル症の病理画像では，無色で幅広く（5～20μm），細胞壁が薄く，隔壁が乏しいリボン状の菌糸および T 字型の分岐菌糸が観察される．教科書的には，アスペルギルス属の特徴とは異なるとされているが，抗真菌薬投与による真菌要素の断片化や強い壊死が起こっている場合，アスペルギルス属であっても菌糸は膨張して不定型となることもあり，同定は困難である．同様に，アスペルギルス属以外の糸状菌に関しても，ムーコルとの鑑別が難しい症例が多い．

ムーコル症の診断には，Calcofluor white 染色（CFWS）による蛍光顕微鏡直接鏡検が簡便で検出に優れていることが示されている[7]．CT 画像所見で深在性真菌症が強く疑われる 61 例のうち，糸状菌の真菌要素が蛍光観察されたのが 49 例あり，隔壁が観察された 36 例はアスペルギルス属，隔壁が無い菌糸が観察された 13 例はムーコルと，49 例全てが培養もしくは遺伝子検査で同定が可能であった[7]．ファンギフローラ染色も同様の検査法である．CFWS は欧州

Fig. 1　真菌同定の流れ～臨床検体から遺伝子同定まで



におけるムーコル症診断治療ガイドラインにおいても推奨されている検査法である[8]．

血清学的診断法は早期診断を可能にする有用な検査である．深在性真菌症のスクリーニング的検査として，わが国で頻繁に行われているβ-D-グルカン検査は，主要な病原真菌に共通する細胞壁の構成成分を検出する方法である．ムーコルはごく微量のβ-D-グルカンしか産生せず，ムーコル症では陰性であることが多い．しかし，陽性となってもムーコル症を否定は出来ない．アスペルギルス症診断に用いられるガラクトマンナン抗原検出法においてもムーコル症では陰性を示し，深在性真菌症が疑われる患者においてガラクトマンナン抗原が陰性となれば，ムーコル症の可能性を支持する根拠になるとされている[8]．以上のように，現時点ではムーコル症診断において有用とされる血清学的診断法は存在しない．

臨床検体からの遺伝子検査法は，分離培養検査よりも迅速であり，様々な検体に応用可能であるが，標準化された方法が無い．さらに，環境からの汚染による誤診の危険性を常に孕んでいる．真菌遺伝子検査における偽陽性の原因として，大きく分けて，サンプル間および外部からの汚染があり，様々な要因を考慮して検査を行う必要がある．商業的なムーコル症遺伝子診断受託は現在のところ無く，ムーコル症が強く疑われる場合，必要であれば専門の施設に相談した方が良い．

分離培養された菌株の遺伝子同定は比較的容易である．核酸精製キットを用いてDNAを抽出精製し，リボゾームRNA遺伝子のinternal transcribed spacer（ITS）領域および26Sリボゾーム RNAのDomain1/Domain2（D1/D2）領域をPCRで増幅し，塩基配列解析を行う．得られた塩基配列についてMycobank（http://www.mycobank.org）やBLAST（http://blast.ncbi.nlm.nih.gov）で検索を行い，基準株と99%以上の高い相同性が認められた場合，当該菌種と判定する．臨床生検サンプルの場合は，細かく刻んだ上でティッシュグラインダーなどを用いて均一化し，プロテイナーゼKを用いて組織を溶解させる．その上で，真菌を破砕するために，細胞壁消化酵素による溶解，もしくはガラスビーズ・ジルコニアビーズによる物理的破砕を行う．核酸精製キットを用いて精製し，上述のITSおよびD1/D2領域のPCRおよび塩基配列解析を行う．この方法では，抽出したDNAにはヒト由来のDNAが大量に含まれており，真菌要素のDNAが極めて少ない，もしくは含まれていない場合，ヒト由来のDNAがPCRで検出されることもあるので，必ず塩基配列解析を行わなければならない．ムーコル症が疑われる症例については，ムーコル特異的プライマーによるsemi-nested PCR[9]を行う．パラフィン包埋病理組織切片では，各社から発売されている専用DNA抽出精製キットを用いる．ホルマリン固定による核酸の分解や蛋白とのクロスリンクにより，500bp以上の増幅を行うPCRは陰性となる可能性が高いため，なるべく短い領域のPCRを行う．パラフィン包埋作業は非無菌的に行われることが多く，環境中の真菌由来の

遺伝子断片の検出に注意を払う必要がある．

3. 得られた検体を培養する場合，検出感度をあげるためにすべきことは？

前述の通り，ムーコル症の症例から菌が分離・同定される率は極めて低く，深在性真菌症ガイドライン 2014 においても培養検査は有用ではないとされている[10]．真菌同定検査においては，分離培養が基本である．原因真菌の菌種同定が可能になり，抗真菌薬感受性試験を行うことにより，治療方針の決定に貢献し，早期治療や予後の向上が期待できる．

推奨する培養方法としては，臨床検体を無菌的に小さく刻み，ポテトデキストロース寒天培地等に軽く押しつけるように載せて，25℃および 37℃で培養を行う．マイコセルなどのシクロヘキシミドを含む培地ではムーコルを含むいくつかの糸状菌の生育を抑制するため，シクロヘキシミドを含まない培地を用いる必要がある．また，ティッシュグラインダーなどによる強力な破砕処理によって，細胞壁の薄いムーコルの真菌要素を殺してしまう可能性があるので注意を要する[11]．

一般的に，ムーコルは 37℃での生育が良好である．25℃よりも 37℃の方が，10 倍程度，嫌気培養からの回復率が高く，また，臨床検体からの培養陽性率が高いことが報告されている[11]．アスペルギルス属に関しても同様の結果が出ている[12]．ムーコルを含む糸状菌の培養陽性率を上げるためには，室温放置の培養だけでなく，37℃の培養も同時に考慮に入れたい．このような理由で，臨床検体からの真菌同定検査を専門施設に依頼する際の検体輸送では，冷温輸送は避けるべきである．

おわりに

ムーコル症を含む深在性真菌症の培養検査および遺伝子検査では，環境の浮遊菌由来の汚染を常に考慮に入れなければならず，臨床症状・画像診断・血清診断・病理診断などの複数の情報から，「総合的に」判断することが重要である．

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CASE REPORT

Disseminated mucormycosis infection after the first course of dose-modified R-EPOCH for advanced-stage lymphoma

Masahito Itoh · Masayuki Oki · Hidetaka Yanagi · Akiko Oka · Sakurako Tajiri · Ryuki Fukuda · Hideki Ozawa · Atsushi Takagi

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Abstract We report the case of a 63-year-old man who presented at our hospital after experiencing fever and dyspnea for more than 1 month. Because his general condition was deteriorating, he was referred to our intensive care unit. He needed critical care and was treated with vasopressors, artificial ventilation, and continuous hemodialysis. Considering his systemic condition, hematological malignancy was suspected. Bone marrow and skin biopsies were performed, and the condition was diagnosed as diffuse large B-cell lymphoma. On the 15th day, suspecting infectious lung disease, we performed bronchoscopy, which showed *Rhizopus* infection. Thus, the patient was administered high-dose liposomal amphotericin B (10 mg/kg) therapy. On the 54th day, he died of a massive pulmonary hemorrhage. Autopsy revealed mucormycosis infection in multiple organs, including the lungs and liver. Vigilance regarding possible mucormycosis infection is required, even after initial chemotherapy in patients whose bone marrow is significantly affected by lymphoma cells and leukemic changes.

Keywords Disseminated mucormycosis · *Rhizopus* · First chemotherapy

Introduction

It is generally considered that mucormycosis is associated with diabetes mellitus (mostly diabetic ketoacidosis), severe hematological malignancy, solid organ or hematopoietic stem cell transplantation, or deferoxamine administration [1]. Mucormycosis may also develop occasionally in immunocompromised patients.

A definitive diagnosis of mucormycosis requires the histopathological identification of organisms in tissue, with culture confirmation. Because tissue biopsy might be difficult to perform in critically ill patients because of a tendency to bleed, mucormycosis is diagnosed in only about half the cases before death [2].

In lymphoma patients, disseminated mucormycosis usually develops after multiple courses of chemotherapy. We encountered a rare case of a patient with lymphoma who developed disseminated mucormycosis after the first course of chemotherapy.

Case report

A 63-year-old man had experienced fever and dyspnea for more than 1 month. He was hospitalized at our affiliated hospital and was treated for community-acquired pneumonia. His general condition did not improve, and consciousness disturbance, respiratory exacerbation, renal dysfunction, and remarkable acidemia caused by metabolic acidosis occurred early in the clinical course.

He was transferred to our intensive care unit (ICU). His medical history included hypertension but not diabetes, and his hypertension was well controlled with amlodipine (5 mg/day) and atenolol (25 mg/day).

On physical examination, the patient's Glasgow coma scale score was E1VTM4, body temperature was 37.8°C, blood pressure was 85/50 mm Hg (dopamine infusion at 5 μg/kg/min), pulse rate was regular at 109 bpm, SpO_2 was 100% on 10 l/min of oxygen via mask, and respiratory

M. Itoh (✉) · M. Oki · H. Yanagi · A. Oka · S. Tajiri · R. Fukuda · H. Ozawa · A. Takagi
Department of General Internal Medicine,
Tokai University School of Medicine, 143 Shimokasuya,
Isehara, Kanagawa 259-1143, Japan
e-mail: egaodon@yahoo.co.jp

rate was 27/min. On auscultation, bilateral moist rales could be heard. Rashes were found over his entire body, mainly on the precordium; this finding had been diagnosed as a drug allergy in the previous hospital. There was pitting edema in both lower extremities. Except these, no abnormal findings were found, and no superficial lymph nodes were palpable.

On laboratory testing, his white blood cell (WBC) count was 2,700/μl (neutrophils 1,782/μl, lymphocytes 351/μl, monocytes 243/μl, lymphoma cells 324/μl), Hb level 8.1 g/dl, platelet (PLT) count 2.0×10^4/μl, aspartate aminotransferase (AST) level 77 U/L, alanine aminotransferase (ALT) level 19 U/l, creatine kinase (CK) level 257 U/l, lactate dehydrogenase (LDH) level 1,285 U/l, creatinine (Cr) level 4.97 mg/dl, blood urea nitrogen (BUN) level 87 mg/dl, uric acid (UA) level 23.2 mg/dl, Ca level 8.6 mg/dl, IP level 14.3 mg/dl, C-reactive protein (CRP) level 15.47 mg/dl, IL-2R level 20,000 U/ml, IgG level 780 mg/dl, IgM level 75 mg/dl, and IgA level 133 mg/dl.

Initial blood glucose level was 131 mg/dl (blood glucose level in the intensive care unit was controlled at about 150–220 mg/dl). HbA1c level was not assessed.

Arterial blood gas analysis was performed while the patient was on 10 l/min via an oxygen mask. Arterial pH was 7.135, PCO_2 was 48.4 torr, PO_2 was 236 torr, HCO_3^- was 15.6 mmol/l, lactate level was 130 mmol/l, and anion gap was 25.2 mEq/l.

Various imaging studies were performed. Chest radiograph and computed tomography (CT) scan of the chest showed left lower lobe consolidation and slight bilateral pleural effusion. Abdominal CT and ultrasonography showed mild hepatosplenomegaly and lymph node swelling of the porta hepatis and the right mesenterium.

At this point, septic shock was diagnosed consequent to nosocomial pneumonia, and the presence of lymphoid malignancy and acute kidney injury caused by sepsis or tumor lysis syndrome was suspected.

Several life support treatments such as vasopressors, artificial ventilation, and continuous hemodialysis were performed in our ICU, and antibacterial agents [tazobactam/piperacillin (2.25 g every 8 h) + ciprofloxacin (200 mg every 12 h), adjusted according to his renal function] were administered.

Because we strongly suspected the presence of lymphoid malignancy and estimated that the tumor burden was large, steroid therapy (prednisone 40 mg/day) was administered at the time of admission. Immediately, bone marrow and skin biopsies were performed, and diffuse large B-cell lymphoma (DLBCL) was diagnosed. His Ann Arbor stage was IV BS, International Prognostic Index (IPI) high, revised IPI poor, and he showed a phenotype of CD5 (+), CD10 (−), CD20 (+), MUM-1 (+), and MIB-1 (high). As per Hans classification, the phenotype was nongerminal center B-cell. This phenotype results in a poor prognosis, and the growth of the tumor was rapid from the high MIB-1 index. The nucleated cell count was 2.6×10^4/μl, and the megakaryocyte count was 15×10^4/μl (myeloblasts 0.6%, lymphoma cells 30.4%).

On the 5th day, initial chemotherapy was administered (dose-modified R-EPOCH: rituximab, 670 mg/day for 6 days; etoposide, 66 mg/day for 4 consecutive days; prednisolone, 80 mg/day for 14 days; vincristine, 0.7 mg/day for 4 consecutive days; cyclophosphamide, 330 mg/day for 5 days; doxorubicin, 17 mg/day for 4 consecutive days). The hematological nadir was reached on the 13th day (leukocyte count 100/μl, neutrophils 48/μl, monocytes 20/μl). The leukocyte count improved to 3,000/μl (neutrophils 2,550/μl, lymphocytes 30/μl, monocytes 330/μl) 1 week later.

The complete blood count improved gradually. On the 25th day, bone marrow obtained from the second biopsy revealed the disappearance of lymphoma cells. We then thought that the disease was in remission.

Fever developed despite administration of a broad-spectrum antibiotic. We suspected fungal catheter-related bloodstream infection, and therefore administered micafungin (100 mg/day) on the 15th day; the dose was further increased to 150 mg/day on the 32nd day. Later, growth of *Candida glabrata* was noted in the blood cultures.

On the 19th day, progressive respiratory failure occurred while fever and increases in sputum production persisted. Therefore, chest CT was obtained; suspecting infectious lung disease, bronchoscopy and bronchoalveolar lavage were performed. In the right lower lobe bronchus, white lesions with destruction of neighboring tissues were detected; therefore, transbronchial lung biopsy was performed (Fig. 1).

After a few days, mucormycosis was suspected based on pathological examination, and this was confirmed when *Rhizopus* species grew in his sputum culture. High-dose liposomal amphotericin B (10 mg/kg) therapy was started. However, after 6 days, black lesions appeared on his nose and his left upper extremity (Fig. 2). Biopsies were obtained from both these lesions, and *Rhizopus* species grew similarly from both. Magnetic resonance imaging (MRI) of the head was performed, and a soft tissue intensity was found in the right accessory sinus cavity.

Because of these infections and the patient's serious general condition, the second course of chemotherapy could not be provided to him. For the same reason, surgical intervention for mucormycosis of his lungs and sinus could not be performed. Micafungin (150 mg/day) was added because disseminated mucormycosis had become worse despite the high-dose liposomal amphotericin B treatment. The total dose of micafungin was 4,650 mg and that of liposomal amphotericin B was 19,200 mg.

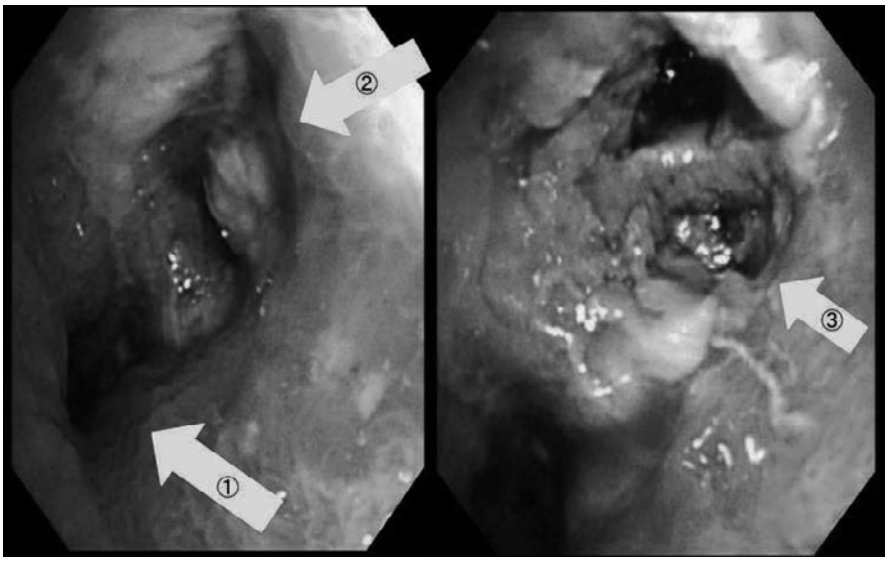

Fig. 1 Bronchoscopy findings: *1*, entry of the middle lobe bronchus; *2*, right lower lobe bronchus; *3*, white lesions with destruction of the neighboring tissues. These lesions were soft and tend to bleed easily. Transbronchial lung biopsy was performed on the same lesions, and *Rhizopus* sp. infection was diagnosed

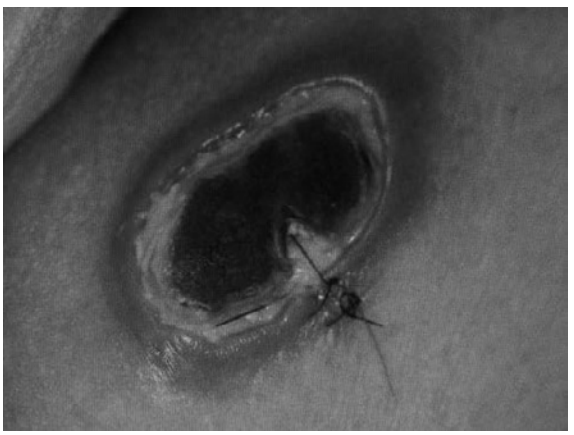

Fig. 2 Black skin lesions on the left upper extremity. Later, a skin biopsy was performed and *Rhizopus* sp. infection was diagnosed

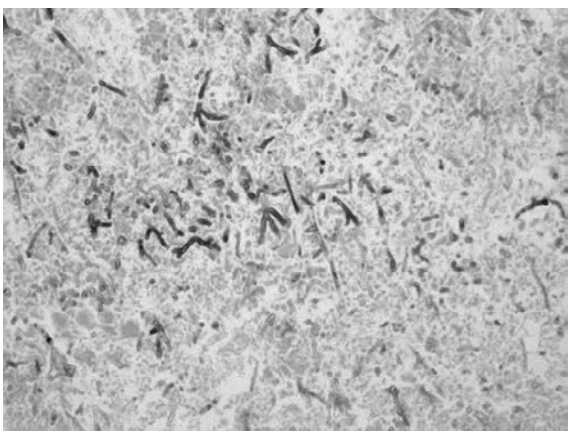

Fig. 3 Many fungi were found in the lung tissue

On the 54th day, the patient died of a massive pulmonary hemorrhage resulting from angio-invasion by mucormycosis. Permission for an autopsy was granted. On final pathology, we found that a few large-sized lymphoma cells existed in the spleen and in the systemic lymph nodes. In terms of disseminated mucormycosis, additional infection sites were found, including the left lung and liver. Many fungi were found in the lung tissue (Fig. 3), nasal mucosa, and skin in each biopsy. Growth of *Rhizopus* species was noted in each culture.

Discussion

Rhizopus species are the most common pathogens of mucormycosis infection. Diabetes is the most common risk factor, found in 36% of cases, followed by hematological malignancies in 17% of cases, and solid organ or hematopoietic stem cell transplantation in 12% of cases [3].

At first glance, it could not be said that there were severe risk factors, for example, long-term lymphoma, multiple-course chemotherapy, or aggressive chemotherapy. However, we consider that the significant invasion of the bone marrow by lymphoma cells and the leukemic changes resulted in a severely immunocompromised status. In addition, we could have estimated in more detail the duration of immunosuppression. Based on the facts that dyspnea had been present for more than 1 month, involvement of the bone marrow was demonstrated, and the first chemotherapy treatment was carried out, the duration of immunosuppression might be several months.

Particularly in patients with lymphoma who have bone marrow infiltration, disseminated mucormycosis can develop even after only one course of chemotherapy. A high index of suspicion is required for this lethal infection. Disseminated mucormycosis occurs most commonly in severely immunocompromised patients, burn patients, premature infants, and patients who have received deferoxamine [4].

During the clinical course of this case, disseminated zygomycosis infection occurred without aggressive chemotherapy or prolonged neutropenia; therefore, this underlying condition cannot be considered a common occurrence.

We believe that the present case is rare in that it involved disseminated mucormycosis, and lymphoma, and developed after only the first chemotherapy.

In this case, there were several risk factors, including chemotherapy (steroids and rituximab), severe neutropenia, renal failure, and hemodialysis. In addition, we consider that the following special factors also played a part.

First, this was not a case of diabetic ketoacidosis, but a remarkable tumor lysis syndrome was found, and together with remarkable acidemia such that persistent blood purification was necessary.

Second, before the onset of disseminated mucormycosis, the patient experienced sepsis from a catheter-related bloodstream infection. We, therefore, began treatment with micafungin at 150 mg every 24 h for *Candida glabrata* infection. A case–control study showed that prior treatment with an antifungal agent such as voriconazole or caspofungin is a risk factor for mucormycosis (odds ratio, 4.41; $P = 0.033$) [5]. Commonly, breakthrough of mucormycosis may develop under the long-term use of voriconazole or caspofungin. In this case, we thought that short-term use may have contributed to the dissemination of the infection from the lung.

Finally, the target glucose level in the critical care unit was higher than that in the regular ward or outpatient department. A large-scale multi-institutional randomized controlled trial showed that a target glucose level of 180 mg/dl or less resulted in lower mortality than did a target of 81–108 mg/dl [6]. Recently, this target has become standard in the ICU. In fact, in our patient, the range of glucose level was about 150–220 mg/dl. We believe that the contribution of glucose level to the likelihood of infection is low, but this glucose level may suggest a slight possibility of being the trigger for the development of mucormycosis.

We encountered a rare case of mucormycosis after first chemotherapy. The case involved a lymphoma patient who exhibited leukemic changes. Because several infections were noted, we concluded that the functions of neutrophils and monocytes were likely to be poor in this patient.

Unfortunately, the functions of neutrophils and monocytes were not analyzed in this case, and the route of infection was not clear; these may be considered as limitations of this case report.

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CASE REPORT

Kei Suzuki · Yumiko Sugawara · Takao Sekine
Kazunori Nakase · Naoyuki Katayama

Breakthrough disseminated zygomycosis induced massive gastrointestinal bleeding in a patient with acute myeloid leukemia receiving micafungin

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Abstract A 69-year-old man, who had been receiving prednisolone for 11 months for treatment of interstitial pneumonia, was diagnosed with acute myeloid leukemia. During induction therapy, he developed severe pneumonia. Although meropenem and micafungin were started, he died of circulatory failure owing to massive gastrointestinal bleeding. Autopsy specimens obtained from the stomach revealed fungal hyphae, which had invaded diffusely into submucosal vessels and caused the massive gastric bleeding. The same hyphae were also observed in both lungs. A diagnosis of disseminated zygomycosis was confirmed by its characteristic histopathological findings. Because zygomycetes are spontaneously resistant to the newer antifungal agents, such as voriconazole or micafungin, it seems likely that the prevalence of zygomycosis as a breakthrough infection may increase in the future. Zygomycosis is a rare, but life-threatening, deep fungal infection that appears in immunologically or metabolically compromised hosts. Its manifestations are clinically similar to those of invasive aspergillosis. In addition to the well-established epidemiology of zygomycosis, this case suggests the following new characteristics. (1) Although the gastrointestinal manifestation of zygomycosis is relatively rare, it is observed more frequently than invasive aspergillosis. (2) Gastrointestinal zygomycosis occasionally leads to the development of necrotic ulcers and may induce hemorrhagic shock.(3) We should be cautious of an occurrence of breakthrough zygomycosis when we use echinocandins for patients with known risk factors, especially steroid use and neutropenia. (4) For patients who are receiving broad-spectrum antibiotics and echinocandins, who are negative for culture studies and aspergillus antigen, and who present with unresolved fever, it is important to make a prompt clinical diagnosis of zygomycosis.

Key words Zygomycosis · Leukemia · Micafungin · Gastrointestinal bleeding

K. Suzuki · Y. Sugawara · T. Sekine
Internal Medicine, Matsusaka Chuo General Hospital, Matsusaka, Mie, Japan

K. Suzuki (✉) · Y. Sugawara · K. Nakase · N. Katayama
Department of Hematology and Oncology, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan
Tel. +81-59-231-5016; Fax +81-59-231-5200
e-mail: keis@clin.medic.mie-u.ac.jp

Introduction

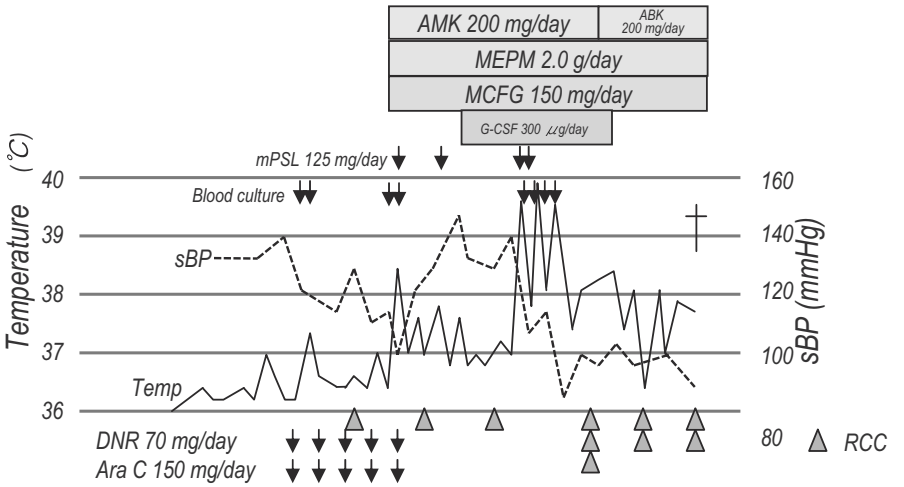
Zygomycosis is a rare, but life-threatening, deep fungal infection that appears in immunologically or metabolically compromised hosts.[1] Because its clinical manifestation is similar to that of invasive aspergillosis, cultures are often negative and no reliable serologic tests are currently available; therefore, antemortem diagnosis is usually difficult. In addition, because zygomycetes are spontaneously resistant to most antifungal agents, except for amphotericin B, it seems likely that zygomycosis might occur as a breakthrough infection associated with the use of newer antifungal agents, such as voriconazole or micafungin. In fact, in the voriconazole era, the incidence of zygomycosis in patients with hematological malignancies has been reported to be increasing.[2,3] Here, we report a case of breakthrough disseminated zygomycosis, which resulted in massive gastrointestinal bleeding, in a patient receiving micafungin.

Case report

A 69-year-old man, with known interstitial pneumonia, was admitted to our hospital with thrombocytopenia and an abnormal leukocyte count and was diagnosed with acute myeloid leukemia (M4 according to the French-American-British [FAB] classification). He had been receiving prednisolone 20–40 mg per day for 11 months to treat persistent respiratory symptoms resulting from the interstitial pneumonia. He also had steroid-induced diabetes mellitus, with a hemoglobin (Hb) A1c level of 7.4%. Induction chemotherapy with idarubicin and cytosine arabinoside for acute leukemia was initiated. On the fifth day after the initiation

of the chemotherapy, he developed sudden dyspnea and had a temperature of 38.9°C. His absolute neutrophil count (ANC) had decreased to 80 μl^{-1}. Physical assessment revealed no infectious focus, and no evidence of infection was found on chest X-rays or on computed tomography (CT) scans. Two sets of blood cultures were negative and no clinically significant organisms grew from sputum cultures. Tests for circulating galactomannan antigen assay and serum 1, 3-β-D-glucan were also negative. However, considering his neutropenic state, the induction chemotherapy was discontinued and empirical treatment with meropenem 2 g per day and micafungin 150 mg per day was started for the treatment of febrile neutropenia. Considering the possibility of a detrimental effect on the underlying interstitial pneumonia related to his febrile condition, intermittent methylprednisolone, 125 mg per day, was initiated to relieve his respiratory condition. Intravenous insulin therapy was also started for his hyperglycemia. On the eleventh day, he had symptoms of severe chest pain and developed respiratory failure. A chest X-ray and CT scan revealed pneumonia in the upper-left pulmonary lobe. These findings were consistent with invasive pulmonary aspergillosis. He was intubated and granulocyte colony-stimulating factor (G-CSF), 300 μg per day, was started. His respiratory condition was stabilized by mechanical ventilation. Because a sputum survey taken from the tracheal tube revealed abundant methicillin-resistant *Staphylococcus aureus* (MRSA) with phagocytosis, arbekacin, an aminoglycoside antibiotic with anti-MRSA activity, was added, at 200 mg per day. On the seventeenth day, because his ANC exceeded 2000 μl^{-1}, G-CSF was discontinued; however, his general condition showed no significant change. On the seventeenth day, he suddenly developed circulatory failure with massive tarry stool and his hemoglobin level decreased, from 9.1 g/dl to 5.4 g/dl. However, his clinical condition did not allow for invasive medical intervention, except for blood transfusions, and he died on the eighteenth day (Fig. 1).

Autopsy findings showed expansion of the stomach with a massive hematoma collection, with mucosal erosion. Microscopic findings revealed many fungi with broad, rarely septate hyphae of uneven diameter, branching at 90° angles and invading tissues with an angiocentric tendency, causing



	admission	Day 1 chemotherapy	Day 5	Day 11 intubation	Day 17 Tarry stool	Day 18 Autopsy
SpO_2 (%)	92	97	96	87	100	98
O_2 delivery (/min)	2l	3l	6l	10l	FiO_2 1.0	1.0
WBC (/μL)	48600	45600	2000	400	6300	41200
Neut (μL)	4860	4560	80	12	2079	1854
HGB (g/dl)	8.2	7.9	8.8	9.4	9.1	5.4
Alb (mg/dL)	3.2		2.8	1.9	1.8	1.9
LDH (IU/L)	948		313	209	393	594
BUN (mg/dL)	12		32	26	28	48
Cr (mg/dL)	0.73		0.54	0.57	0.67	0.94
CRP (mg/dL)	2.7		4.4	17.9	28.4	21.3
1,3-β-D-glucan (pg/ml)	5.56		5.56		5.56	
Aspergillus antigen			(-)	(-)	(-)	
Pneumonia shadow	(-)		(-)	(+)	(++)	

Fig. 1. Clinical course. *AMK*, Amikacin; *ABK*, arbekacin; *MEPM*, meropenem; *MCFG*, micafungin; *G-CSF*, granulocyte colony-stimulating factor; *mPSL*, methylprednisolone; *DNR*, daunomycin; *Ara C*, cytarabine; *RCC*, red cell concentrates, *WBC*, white blood cell count, *Neut*, neutrophil count; *HGB*, hemoglobin; *Alb*, albumin; *LDH*, lactate dehydrogenase; *BUN*, blood urea nitrogen; *Cr*, creatinine; *CRP*, C-reactive protein, *sBP*, systolic blood pressure; SpO_2, pulse oximeter saturation; FiO_2, inspired oxygen fractional concentration

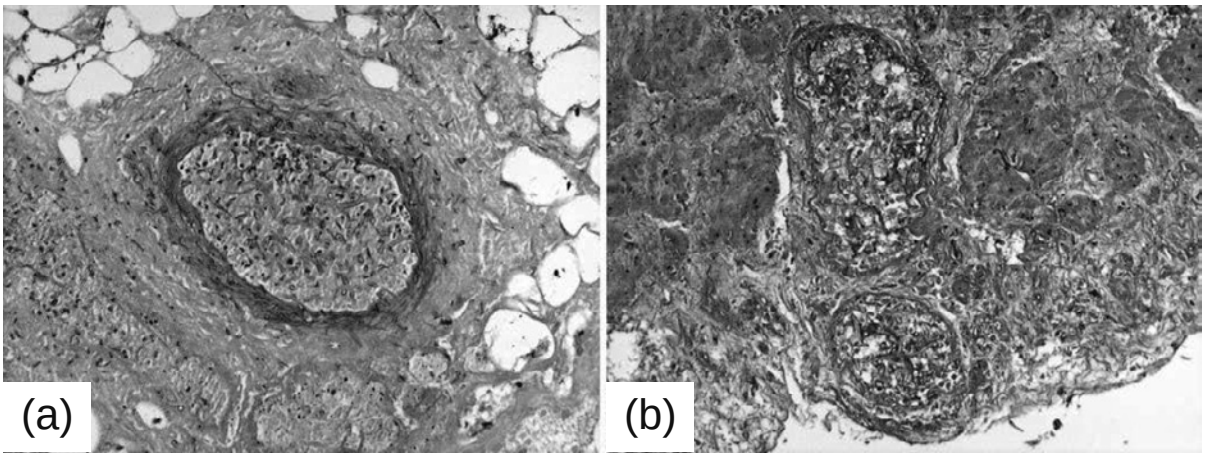


Fig. 2a,b. Histological appearance of an autopsy specimen obtained from the gastric lesion. **a** Numerous fungal hyphae, which were characterized as zygomycetes, were observed in the eroded vascular lesion. **b** Gastric subserous vascular infiltration was also observed. **a** and **b** PAS × 200

infarction, ulceration, and hemorrhagic necrosis (Fig. 2a, b). These fungi invaded diffusely to gastric submucosal vessels and were responsible for the massive gastric bleeding. The same angioinvasive findings of these fungi were observed in both lungs, which showed bacterial pneumonia, probably due to MRSA. Although cultures from an autopsy specimen were unsuccessful, these findings were consistent with zygomycetes, and therefore the histopathological diagnosis was disseminated zygomycosis. Persistent leukemia was detected in the bone marrow.

Discussion

Zygomycosis is a rare life-threatening fungal infection caused by ordinarily avirulent fungi that are widespread in nature. Zygomycosis mainly occurs in immunocompromised hosts, including neutropenic patients with hematological malignancies such as acute leukemia, or in patients under immunosuppressive therapy, particularly after hematopoietic stem cell or solid organ transplantation.[1,4] Additional risk factors include diabetes mellitus; metabolic acidosis; intravenous drug use; iron overload; malnutrition; prior therapy with broad-spectrum antibiotics (including antimycotic therapy with voriconazole or micafungin, as mentioned below), corticosteroids, and deferoxamine; and male sex.[1-5] The primary site of infection at the time of initial diagnosis varies with the underlying disease.[4] Neutropenic patients are at high risk of developing pulmonary infections or disseminated disease, and all of these manifestations are associated with high mortality. Generally, symptoms are nonspecific and antemortem diagnosis is usually difficult. Cultures of sputum or bronchoalveolar lavage fluid show the growth of zygomycetes in only 5% of cases.[6] Moreover, cultures from autopsy or surgical specimens have insufficient sensitivity; these specimens are positive in only 52% and 30% of cases, respectively.[5] Hence, the most sensitive diagnostic procedure for zygomycosis is the identification of the organism in the tissue by histopathology. Although zygomycosis may sometimes be confused with invasive aspergillosis, even histopathologically, it can be diagnosed quite accurately by careful observation. In fact, most cases of zygomycosis in previous reports were diagnosed by histopathology. However, because invasive testing is usually difficult owing to the patient's poor general condition, there is a possibility that many patients with zygomycosis have died but remained undiagnosed. As mentioned above, careful histopathological observation can provide an accurate diagnosis. Therefore, autopsy analysis plays an important role in revealing the epidemiological characteristics of zygomycosis, which is particularly important, given that zygomycosis is clinically quite similar to invasive aspergillosis. However, *Aspergillus sp.* seldom, if ever, involve the gastrointestinal tract; gastrointestinal zygomycosis is rare but is occasionally found in patients with severe malnutrition or after intensive chemotherapy.[1,5,7] Zygomycetes probably enter the host via the mouth, invade the gastrointestinal mucosa, with the development of an ulcer and at times stricture, and enter the circulation from the ulcer in cases of disseminated disease.[8] Therefore, gastrointestinal manifestations such as abdominal pain, hematemesis, or melena are more likely to indicate zygomycosis than aspergillosis. Additionally, during upper gastrointestinal endoscopy, gastrointestinal zygomycosis can be seen as a characteristic dark green hemorrhagic appearance, unlike the white slough of ordinary gastric ulcers.[9] Therefore, these findings might provide significant clues to aid in the diagnosis of zygomycosis. In the present patient, a pulmonary lesion owing to zygomycetes was also observed. However, during his hospitalization, he was cared for under high-efficiency particulate air-filtered conditions. Furthermore, because the gastric mucosa was primarily affected, rather than the lungs, we believe that the infection route in this patient was endogenous via the gastrointestinal tract.

Considering the above-mentioned histopathological findings in the present patient, and considering that endoscopic intervention was not possible because of his hemodynamic instability, it was reasonable to make a diagnosis that the direct cause of death was hemorrhagic shock occurring as a result of gastrointestinal zygomycosis.

We note that, with the new antifungal agents, breakthrough infection is becoming a significant public health problem. For example, breakthrough trichosporonosis related to micafungin is well known.[10,11] Micafungin is a newly approved antifungal agent in the echinocandin class that inhibits the synthesis of 1, 3-β-D-glucan, an essential fungal cell-wall component. Because of its safety and broad spectrum of activity, including against *Candida* and *Aspergillus sp.*, micafungin is widely used in Japan. However, this agent has no activity against zygomycetes or against *Trichosporon* and *Cryptococcus sp*. Because invasive aspergillosis is the most commonly observed pulmonary mycosis in patients with acute leukemia, micafungin was used for 15 days against suspected aspergillosis in the present patient. The lung tissue damage caused by bacterial pneumonia as a result of MRSA probably provided the breakthrough infectious focus for the zygomycetes, which may have selectively proliferated with the use of micafungin. In fact, breakthrough zygomycosis related to voriconazole has already been reported.[2,3,12] Therefore, we should also use echinocandins with care. Our patient had many factors that predisposed to the development of zygomycosis, including acute leukemia, diabetes mellitus, prolonged corticosteroid use, and being male. Unfortunately, because of the relative rarity of this infection, large comparative studies of antifungal agents have not been feasible. Some reports have suggested that posaconazole has efficacy against zygomycosis,[13,14] although its efficacy remains controversial.[15] In retrospect, however, because amphotericin B is still the only reliable antifungal agent against zygomycosis, we should have used a high dose of amphotericin B instead of micafungin.

In summary, it is well known that disseminated zygomycosis is a life-threatening deep fungal infection that commonly occurs in neutropenic or immunologically compromised hosts. Based on our clinical experience, the following characteristics are noted.. (1) Although gastrointestinal manifestation of zygomycosis is relatively rare, it is observed more frequently than invasive aspergillosis. (2) Gastrointestinal zygomycosis occasionally leads to the development of necrotic ulcers and may induce hemorrhagic shock. (3) We should be cautious of the occurrence of breakthrough zygomycosis when we use echinocandins for patients with known risk factors, especially steroid use and neutropenia. (4) For patients who are receiving broad-spectrum antibiotics and echinocandins, who are negative for culture studies and aspergillus antigen, and who present with unresolved fever, it is important to make a prompt clinical diagnosis of zygomycosis.

Based on autopsy results, zygomycosis is the third most common cause of deep fungal infection in patients with leukemia, including myelodysplastic syndrome, and was observed in 5.7%-9.2% of cases of deep fungal infection in such patients.[16] However, although zygomycosis has not shown an upward trend since 2001, the incidence of zygomycosis may increase with the increasing use of the newer antifungal agents in the near future, and we should follow the trends of this disease closely.

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