Medical Mycology Case Reports 8 (2015) 21–23

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Successful treatment of an invasive fungal infection caused by *Talaromyces* sp. with voriconazole

Uluhan Sili [a,*], Huseyin Bilgin [a], Rikesh Masania [b], Emel Eryuksel [c], Nuri Cagatay Cimsit [d], Gulcicek Ayranci [e], Malcolm Richardson [b], Volkan Korten [a]

[a] Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Marmara University, Istanbul, Turkey
[b] Mycology Reference Centre, University Hospital of South Manchester, Manchester, and Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University of Manchester, UK
[c] Department of Pulmonary and Critical Care, School of Medicine, Marmara University, Istanbul, Turkey
[d] Department of Radiology, School of Medicine, Marmara University, Istanbul, Turkey
[e] Department of Pathology, School of Medicine, Marmara University, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 25 December 2014
Received in revised form
6 February 2015
Accepted 23 February 2015
Available online 24 February 2015

Keywords:
Invasive fungal infection
Rheumatoid arthritis
Mold infection
Voriconazole

ABSTRACT

Invasive fungal infections (IFI) are on the rise due to increasing numbers of immunosuppressed and critically ill patients. A malignant-looking pulmonary nodule in an immunosuppressed patient may indeed be caused by a fungal organism. We report a patient, who was eventually diagnosed with an IFI caused by an agent of hyalohyphomycosis, *Talaromyces* sp. determined via molecular methods and succesfully treated with voriconazole.

1. Introduction

The incidence of invasive fungal infections (IFI) has been on the rise due to increasing numbers of immunocompromised or severely ill patients. This rise in incidence is accompanied by a broadening range of fungal species causing potentially lethal disease [1]. The subject of this report had a solitary pulmonary nodule, which was initially suspected to be of malignant origin but eventually was confirmed to be of fungal origin. To our knowledge, this is the first report of an IFI caused by *Talaromyces* species (sp.) that is successfully treated with voriconazole.

2. Case

A 61-year-old male was admitted to our clinic (day 0) with complaints of right pleuritic chest pain and dyspnea on exertion during the past two weeks. He reported increased sputum production and purulence accompanied by cough and fever. He had been diagnosed with rheumatoid arthritis (RA) and chronic obstructive pulmonary disease (COPD) five years ago. His RA was under control with leflunamide 20 mg per day and methylprednisolone 4 mg per day. He used inhaled corticosteroids and bronchodilators for COPD.

On day −150, his rheumatologist had ordered a computerized chest tomography (CT) scan, which revealed a 12-mm nodule with spicular borders in the left lower lobe (Fig. 1). On day −30, this nodule was biopsied by interventional radiology for exclusion of malignancy. As the patient did not have any symptoms compatible with an infectious process at that time, samples were sent for histopathological examination only. Malignancy was ruled out, but the pathology report described a suppurative, granulomatous inflammation around fungal hyphal elements with the presumptive diagnosis of a candida infection (Fig. 2).

On admission, his body temperature was 38 °C, his pulse rate was 90 beats per minute, respiratory rate was 20 per minute and blood pressure was 130/70 mmHg. Oxygen saturation was 98% on room air. Bilateral rhonchi were heard. Remainder of the physical examination was unremarkable. A repeat thoracic CT taken on day 0 revealed persistence of the nodule in left lower lobe, while there was a new loculated pleural collection adjacent to medial right lower lobe (Fig. 3a). Fluconazole (400 mg i.v. once daily) was started with the presumptive diagnosis of candida pneumonia, based on histopathological report.

On day +4, right pleural collection was drained by

* Corresponding author. Fax: +90 216 625 4790.
E-mail address: uluhan.sili@marmara.edu.tr (U. Sili).

http://dx.doi.org/10.1016/j.mmcr.2015.02.002

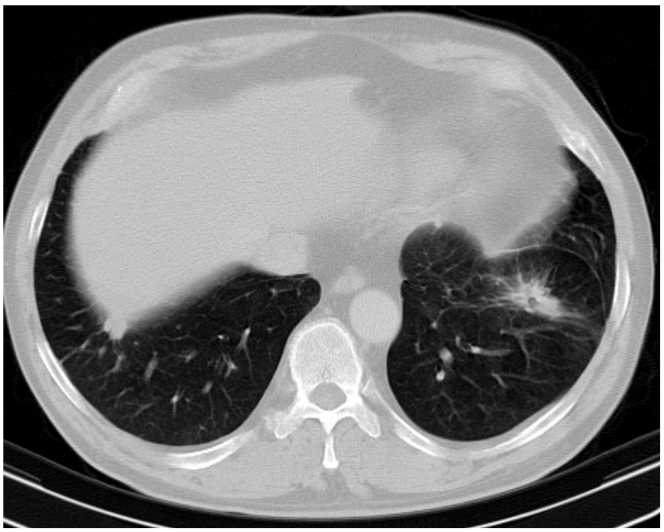

Fig. 1. A 12-mm sub-solid nodule with spicular borders in left lower lobe (day -150).

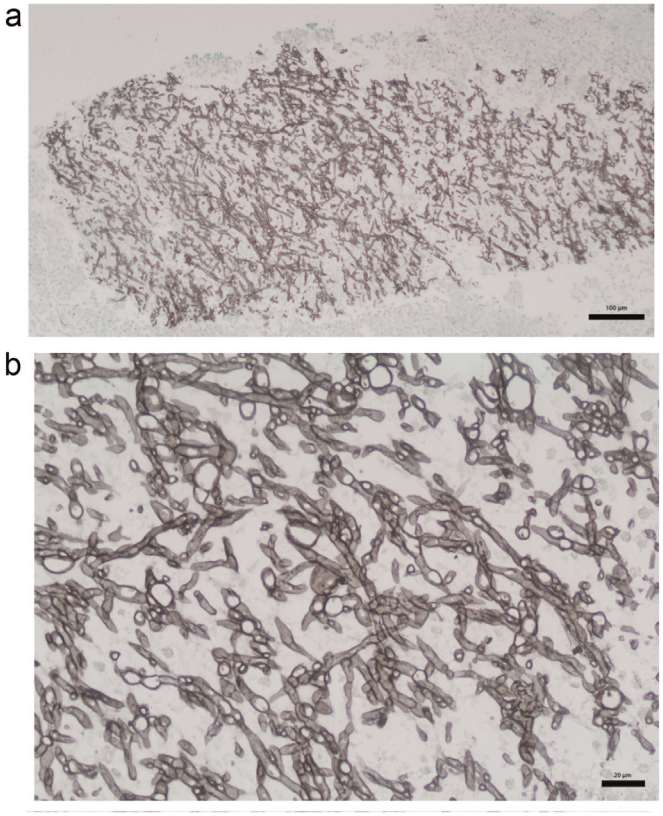

Fig. 2. Grocott's methenamine silver stain; (a) ×100 magnification, (b) ×400 magnification. Suppurative granulamatous inflammation with fungal hyphal elements (day −30).

interventional radiology. Samples sent from this collection were negative for any microbiological growth, but microscopic examination showed abundant polymorphonuclear leucocyte (PMNL) infiltration with a negative Gram stain suggesting abscess formation. Ampicillin-sulbactam (2 g i.v. four times a day) was added to treatment. On day +14, right pleural collection was drained for a second time by thoracic surgery. Samples sent from this collection were again negative for any microbiologic growth, but still showed abundant PMNL infiltration. A thoracic CT taken on day +17 revealed partial regression of right pleural collection,

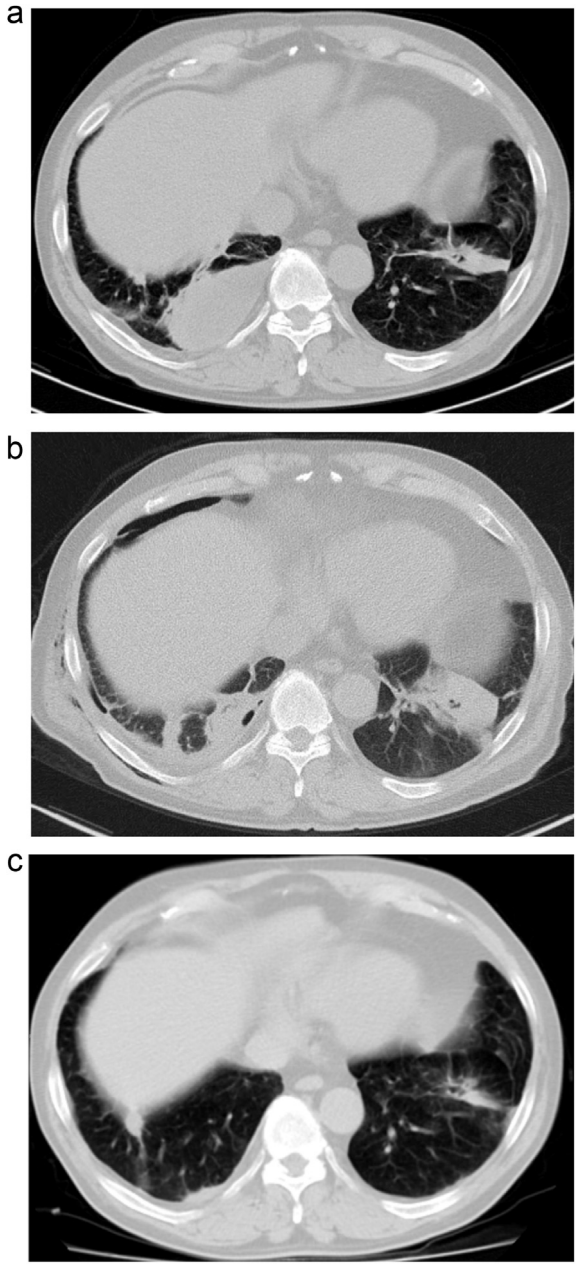

Fig. 3. Thoracic CT imaging at day 0 (a), day +17 (b) and day +82 (c). Image (a) shows left lower lobe nodule and right pleural collection at day 0. Image (b) shows progression of left lower lobe nodule into a consolidation and partial regression of right pleural collection at day +17. Image (c) shows 80% reduction in size of left lower lobe nodule and complete regression of right pleural collection.

while left lower lobe nodule progressed into a focal nodular consolidation (Fig. 3b). We concluded that fluconazole failed. Antifungal treatment was changed to caspofungin (70 mg i.v. loading and 50 mg i.v. maintenance once daily) based on the assumptions of fluconazole unresponsive candida pneumonia or possibility of a mold infection. On day +26, antifungal treatment was switched to voriconazole (400 mg i.v. twice daily loading and 200 mg i.v. twice daily maintenance), since an oral agent would be preferable during the prolonged treatment period.

A control thoracic CT taken on day +31 revealed 50% regression in size of nodule and the patient was discharged with voriconazole 200 mg per oral twice daily. Another control CT taken on day +82 revealed almost complete regression of lesion (Fig. 3c) and voriconazole treatment was stopped on day +99. Patient was given a biological agent, abatacept for RA on day +177 and

completed a total of nine monthly injections without any infectious complications.

Later for identification of the fungus, genomic sequencing from paraffin blocks was conducted. This involved deparaffinization of tissue sample performed as per the protocol described by Bialek et al. [2], and genomic DNA extraction using the CTAB method as described by Fraczek et al. [3]. The fungal ITS region was amplified by PCR using Primers ITS1 and ITS4 [4] and sequenced in both directions by dideoxy chain termination/ cycle sequencing on an ABI 3730XL sequencing machine (Eurofins MWG Operon Ebersberg, Germany). Sequences were compared to those available in the CBS-KNAW Fungal Biodiversity Centre database (http://www.cbs.knaw.nl) using the Pairwise Sequence Alignment tool. The ITS sequence demonstrated 100% identity to *Talaromyces* sp. (GenBank Accession no. JX315670, base pair match 478/478) genus. Although the top species identity was *Talaromyces stollii* (GenBank Accession no. JX965246.1, base pair match 478/478), the ITS region is inadequate to definitively distinguish to this level.

3. Discussion

Our case highlights the need for microbiological examination of solitary pulmonary nodules detected in immunosuppressed patients. Although the major differential diagnosis is malignancy for such nodules, fungal organisms may well be the etiological agent, particularly in immunosuppressed patients. Biopsy is usually performed to rule out malignancy; however, once the specimen is placed in formalin, the opportunity for culture is lost, which is the gold standard in identification of fungal element. As in our case, when culture opportunity is lost or there is no growth in culture, a molecular approach may be quite useful in identification of fungal species.

Histopathological examination is crucial to demonstrate invasiveness of infection, but morphological identification of fungal species should be avoided as it may misidentify the fungal element [5]. It has been reported that in at least 20% of cases, misclassifications of fungal organisms occur in histopathological examination [6]. Yeast-mold differentiation is important for empirical and definitive treatment of fungal infections as it affects the choice of antifungal agent. In our case, based on the presumptive histopathological diagnosis of candida infection, a therapeutic trial with fluconazole was carried out as it has both parenteral and oral formulations, is much cheaper than the other antifungal drugs and has fewer side effects. However, patient's condition did not improve which necessitated switching to an extended-spectrum antifungal agent. An echinocandin or voriconazole are possible alternatives in this case, although the latter has an oral formulation making it ideal for prolonged outpatient therapy. In our case, voriconazole was well-tolerated by the patient and led to total cure of mold infection after two and a half months of treatment.

Using DNA sequencing, fungal element was later identified as a mold belonging to *Talaromyces* sp., which is an agent of hyalohyphomycoses. This finding also explained the unresponsiveness to fluconazole that we initially observed. To the best of our knowledge, this is the first report of an IFI caused by *Talaromyces* sp. Our case shows that *Talaromyces* sp. is the latest addition to a growing list of rare light-colored (hyaline) molds causing serious infection [1,7].

Biological therapies for immune-mediated inflammatory diseases appear to carry increased infectious risks [8]. Abatacept functions as a T-cell co-stimulation modulator. Although it carries a labeled warning regarding the risk of pulmonary infections, in clinical trials the incidence of serious infection appeared lower than that encountered with other biological agents [9]. In our case, although secondary prophylaxis was not administered, there was no recurrence of IFI with abatacept. More studies are needed to determine whether abatacept can safely be given without secondary prophylaxis in patients with proven IFI.

Clinicians taking care of immunocompromised patients should carry the suspicion that a fungal agent might play a role in a variety of disease settings, thus remember to request for microbiological as well as histopathological examination.

Conflict of interest

There are none relevant to this case.

Acknowledgements

We would like to thank Lutfiye Mulazimoglu Durmusoglu, Zekaver Odabasi, Elif Tukenmez Tigen and Nilgun Cerikcioglu for helpful discussion. We would like to thank medical writer Beril Tavsanli Sili, Ph.D. for her help in finalizing the manuscript.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.mmcr.2015.02.002.

References

[1] S.C. Chen, C.C. Blyth, T.C. Sorrell, M.A. Slavin, Pneumonia and lung infections due to emerging and unusual fungal pathogens, Semin. Respir. Crit. Care Med. 32 (6) (2011) 703–716, Epub 2011/12/15.
[2] R. Bialek, F. Konrad, J. Kern, C. Aepinus, L. Cecenas, G.M. Gonzalez, et al., PCR based identification and discrimination of agents of mucormycosis and aspergillosis in paraffin wax embedded tissue, J. Clin. Pathol. 58 (11) (2005) 1180–1184, Epub 2005/10/29.
[3] M.G. Fraczek, M. Bromley, A. Buied, C.B. Moore, R. Rajendran, R. Rautemaa, et al., The cdr1B efflux transporter is associated with non-cyp51a-mediated itraconazole resistance in Aspergillus fumigatus, J. Antimicrob. Chemoth. 68 (7) (2013) 1486–1496.
[4] T.J.B.T. White, S. Lee, J.W. Taylor, Amplification and Direct Sequencing of Fungal Ribosomal RNA Genes for Phylogenetics, in: M.A.G.D.H. Innis, J.J. Sninsky, T. J. White (Eds.), Academic Press, New York: NY, 1990.
[5] J. Guarner, M.E. Brandt, Histopathologic diagnosis of fungal infections in the 21st century, Clin. Microbiol. Rev. 24 (2) (2011) 247–280, Epub 2011/04/13.
[6] A.R. Sangoi, W.M. Rogers, T.A. Longacre, J.G. Montoya, E.J. Baron, N. Banaei, Challenges and pitfalls of morphologic identification of fungal infections in histologic and cytologic specimens: a ten-year retrospective review at a single institution, Am. J. Clin. Pathol. 131 (3) (2009) 364–375, Epub 2009/02/21.
[7] S. Naggie, J.R. Perfect, Molds: hyalohyphomycosis, phaeohyphomycosis, and zygomycosis, Clin. Chest Med. 30 (2) (2009) 337–353 vii–viii. Epub 2009/04/21.
[8] N. Haroon, R.D. Inman, Infectious complications of biological therapy, Curr. Opin. Rheumatol. 21 (4) (2009) 397–403, Epub 2009/05/05.
[9] S.A. Novosad, K.L. Winthrop, Beyond tumor necrosis factor inhibition: the expanding pipeline of biologic therapies for inflammatory diseases and their associated infectious sequelae, Clin. Infect. Dis. 58 (11) (2014) 1587–1598, Epub 2014/03/04.