CASE REPORT

Skin nodules in a patient with acute lymphoblastic leukaemia

Lenaïg Le Clech,¹ Pascal Hutin,² Solène Le Gal,³ Gaëlle Guillermin¹

¹Department of Hématologie, CHRU Brest, Brest, France

²Department of Internal Medicine and Hematology, Inter Communal Hospital Quimper, Quimpercedex, France

³Laboratory of Parasitology and Mycology, CHRU Brest, Brest, France

Correspondence to

Lenaïg Le Clech,
lenaig.leclech@hotmail.fr

SUMMARY

Opportunistic infections cause a significant morbidity and mortality in immunocompromised patients. We describe the case of a patient with skin fusariosis and a probable cerebral toxoplasmosis after UCB stem cell transplantation for B-cell acute lymphoblastic leukaemia. *Fusarium* species (spp) infections are difficult to treat. To date, there has been no consensus on the treatment of fusariosis and the management of its side effects. Given the negative pretransplant *Toxoplasma* serology in this case, identifying the origin of the *Toxoplasma* infection was challenging. All usual transmission routes were screened for and ruled out. The patient's positive outcome was not consistent with that of the literature reporting 60% mortality due to each infection.

BACKGROUND

This case highlights the difficulty to manage febrile neutropenia in haematological malignancy, in particular in a patient presenting a concomitant infection. This case reports a detailed description of the procedures involved in the patient management. We suggest screening of the whole body and performing biopsy when there is a suspicion of abnormality. Clinicians and microbiologists should be warned. In this case, the patient presented a concomitant infection. Fusariosis treatment complications were: the side effects of amphotericin B and the lack of a gold standard of treatment. The identification of the origin of second infection, cerebral toxoplasmosis, was challenging. *Toxoplasma* infection is very rare in seronegative patients before bone marrow transplantation (BMT). All usual transmission routes were screened for and ruled out: bone marrow or blood products, primary infection or reactivation of latent infection.

CASE PRESENTATION

An 18-year-old woman, on remission from a second recurrence of B-cell acute lymphoblastic leukaemia diagnosed at the age of 5, was admitted to our medical hospital university for BMT. She underwent umbilical cord blood (UCB) stem cell transplantation.

Myeloablative conditioning regimen was started and double T-cell immunosuppression agents were given as graft-versus-host disease (GVHD) prophylaxis. Posaconazole was given as fungal prophylaxis. The patient was in aplasia on day 3. Cell graft failure was confirmed on day 42, leading to a second UCB stem cell transplantation. At day 7 from the second transplantation, fever was reported without other known symptoms. Consequently, the

antibiotherapy was combined with an antifungal drug (echinocandin).

INVESTIGATIONS

The blood and urinary cultures were sterile. The long-term catheter was not infected. A chest CT was normal. Fever (40°C) was reported. Later, skin involvement was observed as nodules on the right arm (figure 1) and on both thighs (figure 2). Nodules were 1 cm in diameter, papular or with central necrosis surrounded by an erythematous base.

Pus was collected from one lesion. The sample was dispatched for analysis to bacteriology, virology, parasitology and mycology laboratories.

DIFFERENTIAL DIAGNOSIS

No bacteria were identified (Gram-positive or Gram-negative bacteria, *Nocardia*, *Mycobacteria*). No viruses or parasites were found. Cryptococcal antigen was negative in a serum sample. Galactomannan test was negative and 1,3-β-D-glucan test was not performed. Septate branching hyphae were observed on microscopic examination of the pus using toluidine blue O stain (figures 3–5). Hypothesis of invasive fungal infection caused by *Aspergillus*, *Fusarium* or *Zygomycetes* was made. The patient was still neutropenic (<500 µL).

TREATMENT

Echinocandin was discontinued and empirical therapy with amphotericin B was started. A high dose of liposomal amphotericin B was used (5 mg/kg/day).

OUTCOME AND FOLLOW-UP

Engraftment was conducted on day 23. On day 26, the patient's fever diminished and her lesions

Figure 1 Skin nodules on the right arm.

CrossMark

To cite: Le Clech L, Hutin P, Le Gal S, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-010481

Figure 2 Skin nodules on the thigh.

began to heal. The results from culture were positive, and *Fusarium* spp were identified. Further identification of the species within the *Gibberella fujikuroi* species complex was made by the National Center of reference for invasive mycosis and antifungals (CNRMA, Institut Pasteur Paris). Antifungal susceptibility testing was performed using EUCAST standardised broth microdilution method. The results were as follows: amphotericine B 2 µg/mL; itraconazole >8 µg/mL; voriconazole 4 µg/mL; posaconazole 4 µg/mL and caspofungin 2 µg/mL.

No other lesions were observed: abdominal, chest, brain and sinus CTs were normal. Echocardiography was normal. The long-term catheter was removed and its culture was sterile.

The treatment was continued intravenously for 3 weeks. The patient was hospitalised again on day 43 for seizure and acute renal failure with severe hypokalaemia. Cyclosporine was discontinued and amphotericine B was replaced with oral voriconazole. Lymphocytic meningitis was found through microscopic

Figure 3 Direct examination of the sample showed septate branching hyphae.

Figure 4 Macroscopic culture of *Fusarium* species (*Gibberella fujikuroi*) on Sabouraud medium at +35°C.

examination of the cerebrospinal fluid (CSF). The parameters of lymphocytic meningitis revealed eight leucocytes, of which 90% were lymphocytes and 10% were monocytes. The CSF proteins were recorded without any hypoglycorrhachia at 0.65 g/L. *Toxoplasma gondii* DNA was detected in the CSF using a real-time PCR assay. Testing for other causes of meningitis was negative (PCR JC virus, adenovirus, HHV6, HHV8, HSV1, HSV2, CMV, enterovirus, BK virus, meningococci, pneumococci and listeria). MRI of the brain was normal. A treatment for *T gondii* with pyrimethamine—sulfadiazine as well as mycophenolate mofetil as GVHD prophylaxis were given.

A new nodular lesion was observed on her arm, but no fungus was detected. Amphotericine B was restarted and the patient's condition remained stable. No acute renal failure was noted at this time. No surgical treatment was recommended by the dermatologist. The treatment was relayed with oral voriconazole on day 98 and wound healing was observed. No recurrence of fusariosis was observed.

DISCUSSION

This patient presented a severe case of immunosuppression. She has been treated with B-cell depleting (BCD) chemotherapy agents several times. In addition, she presented with T-cell immunosuppression due to transplant procedure and GVHD prophylaxis. She presented opportunistic co-infection: skin disseminated fusariosis and cerebral toxoplasmosis.

Fusarium spp being one of the most important plant pathogens can cause a broad spectrum of infections in humans. These species are known to be present in soil, underground and aerial plant parts, plant waste and water. Our immunity system plays a major role in fighting against fungi and other pathogenic microorganisms. *Fusarium* hyphae can get affected by macrophages and neutrophils. T-cell defense mechanisms are important in fighting against fungi, given the role of Toll-like receptors in the innate immune recognition of fungi.¹

Figure 5 Culture of *Fusarium* species (*Gibberella fujikuroi*) with microscopic view.

Immunosuppressed patients at high risk for infections such as fusariosis are those presenting with severe T-cell immunodeficiency and/or prolonged and profound neutropenia.¹ Infections could be superficial, locally invasive or disseminated. The clinical forms depend on the immune status of the host. Immunocompromised population (haematological malignancy: leukaemia, haematopoietic stem cell transplantation (HSCT),² GVHD; solid organ transplantation) suffer from disseminated infection.

The overall incidence of fusariosis is 6 cases/1000 HSCTs.¹ These HSCTs are mostly hosts of mismatched related donor allogeneic HSCT. The airways are regarded as the main entry route, followed by the skin (onychomycosis). *Fusarium* infections have a trimodal distribution (early, during neutropenia; day 40–70 and > 1 year after receipt of HSCT²).

The clinical presentation depends on the fungi entry route, the intensity and duration of immunosuppression: endophthalmitis, sinusitis, pneumonia (nodular, cavitary lesions, alveolar or interstitial infiltrates), skin involvement (painful erythematous papular or nodular lesions with or without central necrosis, cellulitis, ulcer) and the infection type: fungemia or disseminated.³ A 70% prevalence of skin manifestations has been reported among fusariosis cases.¹ However, Nucci *et al* reported that *Fusarium* infection could rise from only 55% of these lesions.

According to Campo *et al*⁴ nodular lesions represent 53% of the skin abnormalities. Skin biopsy leads to a high diagnostic yield. This provides a direct examination of the filaments present in the skin scrapings. Furthermore, the culture of such filaments is fast and readily conducted.

Fusariosis is categorised according to the revised European Research and Treatment of Cancer Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycosis Study Group (EORTC/MSG) in possible, probable or proven infection.⁴

Global mortality rates are 60–70% at 12 weeks.⁴ Predictors of poor outcome are persistent neutropenia and corticosteroid therapy.

Diagnosis can be made by blood culture, direct clinical examination and tissue culture (hyaline and septate filaments that typically dichotomise in acute angles). The clinicians and the microbiologists must be cautious. *Fusarium* spp propagates fast and readily. The 1,3-β-D-glucan test can be used for invasive *Fusarium* infections identification but this cannot distinguish *Fusarium* from other fungal infections.

There is no gold standard treatment for fusariosis. Antifungal susceptibility testing is necessary. The different species may have different patterns of susceptibility in vitro. Echinocandine have no action. The amphotericin B lipid complex is usually used. An average daily dose of 4.5 mg/kg has been reported for a response rate of 46%. Success rates of 45–48% with voriconazole or posaconazole have been reported.^{3 5 6} However, there have been a few cases of fusariosis reported in the literature when using voriconazole or posaconazole prophylaxis for other indications.^{7 8} Data on combination therapy with a possible synergistic action are limited, especially during the neutropenic phase.^{9–13}

The optimal management includes surgical resection of infected parts and the removal of venous catheters. The probable use of granulocyte-CSF or granulocyte transfusions can be used in complement to antifungal treatment for an optimal patient care.

The treatment should be extended because of relapse. Therapeutic drug monitoring should be carried out for dose adjustment. The type of antifungal should be chosen taking into account patient's characteristics: comorbidities (renal dysfunction), concomitant medications (interactions), gastrointestinal disorders and previous antifungal therapy.

The second infection was cerebral toxoplasmosis. *T gondii* is an ubiquitous intracellular protozoan parasite.

Toxoplasmosis is regarded as a rare but often fatal complication in BMT hosts. In the latter, toxoplasmosis is usually the result of reactivation of latent infection rather than to primary infection. The incidence of toxoplasmosis after BMT has been reported to be approximately 5%.^{14 15} However, this incidence is correlated with the prevalence of *T gondii* in the general population.

Table 1 *Toxoplasma* serology of the patient

Toxoplasma serology	Before transplantation	Between two transplantations	After transplantation, seizure	After transplantation, month 2	After transplantation, month 7
IgM*	Negative (0.06)	NEG (0.06)	NEG (0.11)	NEG (0.07)	NEG (0.04)
IgG†	NEG (0.6 UI/mL)	NEG (1.4 UI/mL)	Positive (3.1 UI/mL)	Equivocal (1.7 UI/mL)	NEG (0.9 UI/mL)
Ig total‡	NEG (1.64)	POS	POS	POS	POS
Western blot IgG§	Not tested	NEG (2 bands)	POS (3 bands)	NEG	NEG
IgM ISAGA¶	Not tested	NEG	NEG	NEG	Not tested
First unit umbilical cord blood: <i>Toxoplasma</i> serology negative			Second unit umbilical cord blood: <i>Toxoplasma</i> serology positive		

*Test ARCHITECT TOXO IgM ELISA Abbott diagnostic. <0.50 NEG. >0.60 POS.

†Test ARCHITECT TOXO IgG ELISA Abbott diagnostic. <1.6 NEG. 1.6–2.9 equivocal. >3.0 POS.

‡Test Toxocompetition VIDAS BioMérieux (Ig Total). >1.60 NEG. <1.60 POS.

§Western blot TOXO II IgG LDBio Diagnostics.

¶Test ISAGA IgM BioMérieux.

The central nervous system, lungs and heart are the most frequently affected organs. The infection is often disseminated in immunosuppressed patients.

Toxoplasmosis occurs mainly in pretransplant seropositive recipients and only a few cases have been reported in seronegative patients.¹⁶ Risk factors are positive pretransplant serology, GVHD, TBI in the conditioning regimen or T-cell depletion. A toxoplasmosis-related mortality rate of 66% has been reported in a previous study.¹⁷

Previous literature has proposed four definitions of post-BMT toxoplasmosis.¹⁸ According to this classification, patients who had a positive PCR in blood without any evidence of organ involvement or seroconversion were classified as having *Toxoplasma* infection. Those who had radiological evidence and respond to anti-*Toxoplasma* therapy were classified as having a possible *Toxoplasma* disease. Patients who had radiological and clinical evidence with one positive PCR were classified as having probable *Toxoplasma* disease. And those who had histological or cytological evidence of tachyzoites in tissue samples were classified as having definite *Toxoplasma* disease.

In this case, the patient was considered seronegative before transplant and received a seropositive transplant. Cerebral toxoplasmosis occurred on day 43 after second BMT, with seizure and fever. Radiological tests were normal. CSF samples were examined using microscopy and PCR. The test results were respectively lymphocytic meningitis and positive toxoplasmosis. However, a low parasite burden was presumed, given that the PCR was positive at the 41st amplification cycle.

Finding the origin of the toxoplasmosis was still a challenge, that is, whether a primary infection or a reactivation. The patient's sera were retrospectively tested at different times: before the first transplant, between the two transplants and after the second transplant (table 1).

Before transplantation, anti-*Toxoplasma* IgG and IgM were negative. Total anti-*Toxoplasma* immunoglobulins were negative but too close to the threshold. Between the two transplants, total anti-*Toxoplasma* immunoglobulin became positive, while IgM and IgG were negative. After the second transplant, IgG and IgM antibody testings were, respectively, weakly positive and negative.

As a result, a primary infection was less likely. The anti-*Toxoplasma* IgM remained negative and no significant rise of anti-*Toxoplasma* IgG was observed. The serology of the donors was tested and the transmission of infection via marrow or blood products was ruled out. Positive IgG serology could be caused by the transfer of transplant's anti-*Toxoplasma* IgG immunity. The last hypothesis was a reactivation of a chronic *Toxoplasma* infection. This could be explained by the latent seronegativity of our patient presenting a severe immunosuppression.¹⁴ In the present case, the 6-month post-transplant *Toxoplasma* serology was reported to be equivocal, consistent with the pre-second-transplant serology.

The lesson to learn here is that opportunistic infections should always be anticipated in immunocompromised hosts presenting: a profound BCD (humoural immunity), T-cell depletion (cellular immunity) and prolonged and profound neutropenia (innate immunity) This case gave a detailed description of the procedures involved in the management of a severe immunocompromised host suffering from opportunistic coinfection. We suggest screening of the whole body and performing biopsy when there is a suspicion of abnormality. The clinicians and microbiologists should be warned. Given the absence of gold standard of treatment for fusariosis, the choice of treatment (between amphotericin B, or voriconazole or the combination)

should be finalised taking into account the patient's characteristics and risk factors. Dosing of fusariosis therapeutics should be high along with close drug monitoring. It is worth mentioning that neutrophil count recovery in these patients indicates patient's positive prognosis.

Pretransplant *Toxoplasma* serology can be falsely negative in a former immunocompromised host. The patient's education becomes mandatory, for instance, in pregnant women to prevent this infection. In such cases of pretransplant false-negative *Toxoplasma*, a tailored chemoprophylaxis can be proposed.¹⁸

Learning points

- ▶ During febrile neutropenia, a biopsy of any new skin lesions should be done. Samples should be dispatched for analysis to bacteriology, virology, mycology and parasitology laboratories. The microbiologist must be alerted.
- ▶ Filamentous fungal infection can occur when fever is persistent despite combined antibiotherapy and antifungal therapy (echinocandin).
- ▶ Incidence of resistant filamentous fungi is increasing (fusariosis, mucormycosis, scedosporiosis).
- ▶ Pretransplant *Toxoplasma* serology can be falsely negative in a former immunocompromised host. The patient's education becomes mandatory, for instance, in pregnant women to prevent this infection.

Acknowledgements The authors would like to thank Dr Dorothée Quinio, Mathieu Grégoire (parasitology and mycology laboratories CHRU Brest), Zarrin Alavi (INSERM CIC 0502, CHRU Brest) and Pascaline Rameau (RIMBO Quimper unit, CHIC Quimper) for their precious advice in writing this case report.

Contributors LLC: wrote the article, treated the patient. GG: reviewed the article, treated the patient. PH: reviewed the article. SLG: help to biologic diagnose.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Nucci M, Anaissie E. Fusarium infections in immunocompromised patients. *Clin Microbiol Rev* 2007;20:695–704.
- 2 Nucci M, Marr KA, Queiroz-Telles F, et al. Fusarium infection in hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2004;38:1237–42.
- 3 Nucci M, Anaissie E. Cutaneous infection by Fusarium species in healthy and immunocompromised hosts: implications for diagnosis and management. *Clin Infect Dis* 2002;35:909–20.
- 4 Campo M, Lewis RE, Kontoyiannis DP. Invasive fusariosis in patients with hematologic malignancies at a cancer center: 1998–2009. *J Infect* 2010;60:331–7.
- 5 Lortholary O, Obenga G, Biswas P, et al. International retrospective analysis of 73 cases of invasive fusariosis treated with voriconazole. *Antimicrob Agents Chemother* 2010;54:4446–50.
- 6 Raad II, Hachem RY, Herbrecht R, et al. Posaconazole as salvage treatment for invasive fusariosis in patients with underlying hematologic malignancy and other conditions. *Clin Infect Dis* 2006;42:1398–403.
- 7 Bose P, Parekh HD, Holter JL, et al. Disseminated fusariosis occurring in two patients despite posaconazole prophylaxis. *J Clin Microbiol* 2011;49:1674–5.
- 8 Cudillo L, Girmenia C, Santilli S, et al. Breakthrough fusariosis in a patient with acute lymphoblastic leukemia receiving voriconazole prophylaxis. *Clin Infect Dis* 2005;40:1212–13.
- 9 Ho DY, Lee JD, Rosso F, et al. Treating disseminated fusariosis: amphotericin B, voriconazole or both? *Mycoses* 2007;50:227–31.
- 10 Tortorano AM, Prigitano A, Dho G, et al. Species distribution and in vitro antifungal susceptibility patterns of 75 clinical isolates of Fusarium spp. from Northern Italy. *Antimicrob Agents Chemother* 2008;52:2683–5.
- 11 Córdoba S, Rodero L, Vivot W, et al. In vitro interactions of antifungal agents against clinical isolates of Fusarium spp. *Int J Antimicrob Agents* 2008;31:171–4.

- 12 Neuburger S, Massenkeil G, Seibold M, *et al.* Successful salvage treatment of disseminated cutaneous fusariosis with liposomal amphotericin B and terbinafine after allogeneic stem cell transplantation. *Transpl Infect Dis* 2008;10: 290–3.
- 13 Jossi M, Ambrosioni J, Macedo-Vinas M, *et al.* Invasive fusariosis with prolonged fungemia in a patient with acute lymphoblastic leukemia: case report and review of the literature. *Int J Infect Dis* 2010;14:e354–6.
- 14 Fricker-Hidalgo H, Bulabois C-E, Brenier-Pinchart M-P, *et al.* Diagnosis of toxoplasmosis after allogeneic stem cell transplantation: results of DNA detection and serological techniques. *Clin Infect Dis* 2009;48:e9–15.
- 15 Martino R, Bretagne S, Einsele H, *et al.* Early detection of *Toxoplasma gondii* infection by molecular monitoring of *Toxoplasma gondii* in peripheral blood samples after allogeneic stem cell transplantation. *Clin Infect Dis* 2005;40:67–78.
- 16 Bautista G, Ramos A, Forés R, *et al.* Toxoplasmosis in cord blood transplantation recipients. *Transpl Infect Dis* 2012;14:496–501.
- 17 Mele A, Paterson PJ, Prentice HG, *et al.* Toxoplasmosis in bone marrow transplantation: a report of two cases and systematic review of the literature. *Bone Marrow Transplant* 2002;29:691–8.
- 18 Martino R, Maertens J, Bretagne S, *et al.* Toxoplasmosis after hematopoietic stem cell transplantation. *Clin Infect Dis* 2000;31:1188–95.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow