BMJ

BMJ 2012;345:e8296 doi: 10.1136/bmj.e8296 (Published 13 December 2012)

ENDGAMES

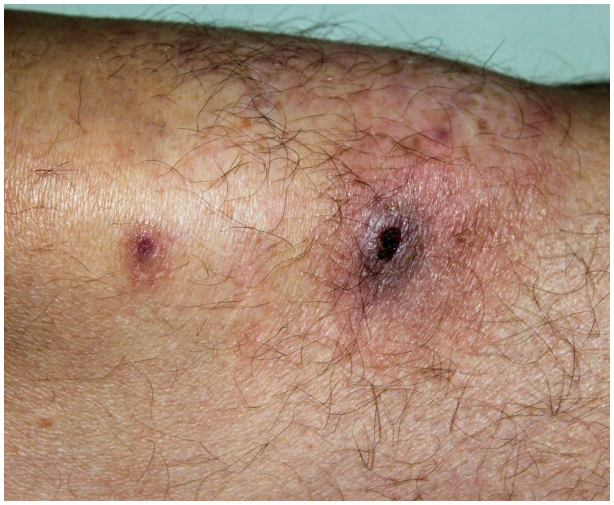
PICTURE QUIZ

A rash in a patient with neutropenia

R T Woolf *specialist registrar dermatology*[1], T Yeghen *consultant haematologist*[2], H du P Menagé *consultant dermatologist*[1]

[1]Department of Dermatology, University Hospital Lewisham, Lewisham Healthcare NHS Trust, London SE13 6LH, UK; [2]Department of Haematology, University Hospital Lewisham

A 72 year old man with relapsed acute myeloid leukaemia developed a rash seven days after starting a combined chemotherapy regimen (fludarabine, cytarabine, granulocyte colony stimulating factor, and idarubicin). He first noticed a painful lesion on his left forefoot, and over the next seven days he developed similar lesions on the left lower limb (fig 1), right thigh, and face. He was referred for a dermatological opinion on day 14.



He was pancytopenic, with undetectable neutrophils and lymphocytes. No prophylactic antibacterial or antifungal drugs had been given. On the fifth day after chemotherapy he had developed a fever with new consolidation on chest radiography. He had been started on empirical broad spectrum antibiotics (piperacillin-tazobactam and gentamicin, with the addition of teicoplanin on day 10 owing to meticillin resistant *Staphylococcus aureus* being cultured in sputum). Despite this, he remained febrile, with worsening inflammatory markers (C reactive protein 270 mg/L; reference range <5 mg/L; 1 mg/L=9.52 nmol/L) and was being managed in an isolation room. He was otherwise asymptomatic and remained stable from a cardiovascular point of view. Chest computed tomography on day 14 showed bilateral multifocal consolidation with faint peripheral halos.

Questions

1 How would you describe the morphology of the presenting rash?

2 What is the most likely diagnosis?

3 What would you consider in your differential diagnosis?

4 What additional diagnostic investigations could you consider?

5 How would you treat this patient?

Answers

1 How would you describe the morphology of the presenting rash?

Short answer

There are two annular macular erythematous lesions overlying the left knee. The largest is about 3 cm in diameter and has a dusky necrotic centre. The smaller 1 cm lesion also has a darker centre.

Long answer

Overlying the left knee there are two annular macular erythematous lesions. The largest measures about 3 cm in diameter and has a dusky necrotic centre. The smaller 1 cm lesion also has a darker centre. These lesions could be described as having a “targetoid” appearance.

2 What is the most likely diagnosis?

Short answer

A persistent fever in a neutropenic patient, which does not respond to broad spectrum antibiotics, raises the possibility of

Correspondence to: R Woolf richard.woolf@kcl.ac.uk

an invasive fungal infection. The development of multiple randomly distributed and centrally necrotic skin lesions with lung consolidation is classic for disseminated *Fusarium* infection. *Fusarium* spp are ubiquitous environmental moulds that are an increasingly common cause of opportunistic infection in immunocompromised patients.

Long answer

A persistent fever in a neutropenic patient, which does not respond to broad spectrum antibiotics, should raise the possibility of an invasive fungal infection. The development of multiple, randomly distributed, painful, and centrally necrotic skin lesions with lung consolidation is classic for disseminated *Fusarium* infection.

Fusarium spp are common saprophytic moulds found in the environment (soil and water). They are important plant pathogens but can also cause a range of infections in humans, which are classified as superficial, locally invasive, or disseminated in nature.[1] The most common species causing invasive infection in humans is the *Fusarium solani* species complex.[2] Disseminated fusarial infection occurs almost exclusively in severely immunosuppressed patients with prolonged neutropenia or T cell immunodeficiency (or both), such as patients who have had chemotherapy or a haematopoietic stem cell transplant.[3 4] In patients who have had solid organ transplants and haematopoietic stem cell transplants, *Fusarium* spp are an increasingly common cause of invasive fungal infections, with *Candida* spp and *Aspergillus* spp being the most common.[5-7] In most cases the portal of entry is not known, although inhalation, ingestion, and entry through sites of skin trauma (such as intravenous lines) have been suggested.[4] Disseminated fusarial infection has also been described in immunocompetent people after extensive burns.[8]

Disseminated *Fusarium* infection most commonly affects the skin (68-91% of cases). Skin lesions typically develop over a few days as painful subcutaneous nodules or centrally necrotic erythematous lesions (ecthyma-like), which can blister.[3 4 6] The variation in morphology probably reflects lesions at different stages of development. Other skin signs associated with disseminated *Fusarium* infection include onychomycosis, paronychia, and digital cellulitis, possibly indicating a site of entry or source for this pathogen.[3] Some haematologists screen for and treat onychomycosis before starting chemotherapy.[2] *Fusarium* infection also commonly affects the respiratory tract. It may cause respiratory symptoms or be diagnosed as consolidation on radiological imaging.[3 4 6] Other clinical features may include sinusitis, myositis, and central nervous system involvement.

3 What would you consider in your differential diagnosis?

Short answer

The differential diagnosis for multiple macular centrally necrotic skin lesions includes bacterial soft tissue infection (such as ecthyma or ecthyma gangrenosum), other invasive fungal infections (such as *Aspergillus* or *Candida*), and cutaneous vasculitis.

Long answer

The differential diagnosis for multiple macular centrally necrotic skin lesions includes other soft tissue infections. These include bacterial infections such as ecthyma, caused by group A β haemolytic streptococci, or the more necrotic and ulcerative ecthyma gangrenosum, caused by *Pseudomonas aeruginosa*. Ecthyma results from direct inoculation of bacteria through the epidermis, whereas ecthyma gangrenosum is caused by haematogenous seeding of *P aeruginosa* after bacteraemia.[9]

A bacterial infection would be unlikely in our case because he was already taking broad spectrum antibiotics. Such skin lesions could be caused by other invasive fungal infections, although skin involvement is uncommon (<10%) in disseminated *Candida* or *Aspergillus* infection.[4] In addition, cutaneous *Candida* infection does not usually have the same targetoid necrotic appearance, and cutaneous *Aspergillus* infection is usually more localised, causing larger areas of necrotic ulceration.[4] Viral infection, such as herpes simplex, should also be considered, although this would be an unusual presentation. The differential diagnosis also includes a necrotising vasculitis or cryoglobulinaemia.[9]

4 What additional diagnostic investigations could you consider?

Short answer

Perform a comprehensive screen for bacterial and fungal infection. This should include skin swabs from an ulcerated lesion, blood cultures, and skin biopsy (for histology and tissue culture). An echocardiogram should be performed to exclude infective endocarditis. With evidence of lower respiratory tract consolidation, bronchoalveolar lavage could be considered.

Long answer

Perform a comprehensive screen for bacterial and fungal infection. This should include skin swabs from an ulcerated lesion, skin biopsy (for histology and tissue culture), and blood cultures. Histological examination of the skin may demonstrate septate fungal hyphae, which often infiltrate cutaneous vessels to cause an occlusive thrombosis. Although septate hyphae are not specific to *Fusarium* spp (they are also seen in aspergillosis), their presence will help guide the decision to start broad spectrum antifungal drugs. The presence of thick walled intercalary hyphal cells, which are uncommon in aspergillosis, on microscopy is also suggestive of *Fusarium* hyphae. Blood cultures are often positive (~40%) in disseminated *Fusarium* infection, especially if the skin is affected (60%), whereas blood cultures are usually negative in aspergillosis.[2 4] When cultured from blood or skin biopsy specimens, *Fusarium* typically produces banana shaped multi-septate macronidia structures, which are characteristic of the species. A polymerase chain reaction assay is often needed for subspecies identification.[2] If there is evidence of lower respiratory tract consolidation, bronchoalveolar lavage could be considered. Samples should be examined by microscopy using bacterial and fungal stains and cultured for bacteria and fungi. The measurement of galactomannan concentrations in serum or bronchoalveolar lavage fluid can aid the diagnosis of aspergillosis,[10 11] although serum assays can also be positive in *Fusarium* infection.[12] An echocardiogram should be performed to exclude infective endocarditis if there is clinical evidence of haematogenous seeding of an infective pathogen. To exclude viral infection, take skin swabs for viral DNA polymerase chain reaction assay.

5 How would you treat this patient?

Short answer

International and national guidelines exist for the management of invasive fungal infections in patients with haematological cancer. First line empirical antifungal agents primarily target

Aspergillus and *Candida*. *Fusarium* is typically resistant to echinocandins (such as caspofungin), so if this organism is considered in the differential diagnosis, liposomal amphotericin B would be a suitable first line agent. Specialist local microbiologist advice should be sought.

Long answer

Many systemic antifungal agents are available for the management of invasive fungal infections. These include polyenes (amphotericin B deoxycholate and liposomal amphotericin B), triazoles (fluconazole, voriconazole, and posaconazole), and echinocandins (caspofungin). These agents differ in their spectrum of activity, pharmacokinetics, dynamics, side effect profile, and cost, all of which will influence the choice of agent.

International and national guidelines exist for the management of invasive fungal infections in patients with haematological cancer,[13-15] although specific management recommendations vary.[16] First line empirical antifungal treatment (liposomal amphotericin B or caspofungin) is primarily targeted at *Aspergillus* and *Candida*, the most common causes of invasive fungal infection in these patients.[13-15] Good quality clinical trial data on antifungal agents for *Fusarium* infection are lacking. The whole genus is resistant to fluconazole and echinocandins, but in vitro susceptibilities to other agents vary between species.[2] Thus in vitro susceptibility testing or *Fusarium* spp identification is important.[2] Liposomal amphotericin B is a suitable first line agent if disseminated *Fusarium* infection is suspected.[2 15] Voriconazole monotherapy has also been used successfully in invasive *Fusarium* infection.[17] Recommendations on combination antifungal regimens for invasive fungal infections are inconsistent.[15] Salvage regimens for disseminated *Fusarium* infection include posaconazole.[15]

Despite the use of single agents or combination antifungals the prognosis of disseminated *Fusarium* infection is poor, with a mortality rate of 50-80%.[3 4 6 18] Persistent neutropenia and the use of systemic corticosteroids are the most important predictors of death.[18 19] Antifungal prophylaxis is recommended for certain high risk haemato-oncology patients, although the definition of this patient cohort varies between guidelines.[16] Some authors advocate specific measures to limit exposure to *Fusarium* spp, including avoiding environmental *Fusarium* reservoirs (such as tap water and soil) and good skin care to prevent pathogen entry, with the aim of preventing infection,.[2]

Patient outcome

Intravenous liposomal amphotericin B (3 mg/kg) was added to his antibiotic regimen because of clinical evidence of a disseminated fungal infection. A skin biopsy showed features of thrombotic vaso-occlusive vasculopathy, with a striking perivascular infiltrate and suppurative granulomas (fig 2). Intravascular ovoid structures were seen on fungal stains (periodic acid Schiff and Grocott's methenamine silver; figs 3 and 4), in keeping with thick walled intercalary hyphal cells seen in *Fusarium* infection. Microscopy of peripheral blood demonstrated macronidial structures that on isolation and culture were identified as *Fusarium* spp.

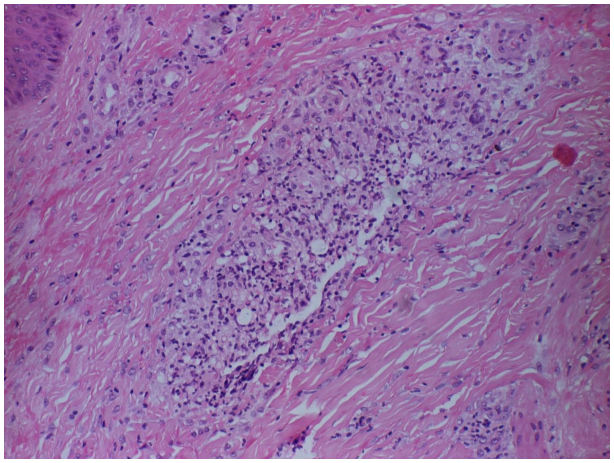


Fig 2 Medium power view of skin biopsy stained with haematoxylin and eosin showing features of a thrombotic vaso-occlusive vasculopathy with perivascular infiltrate and suppurative granulomas

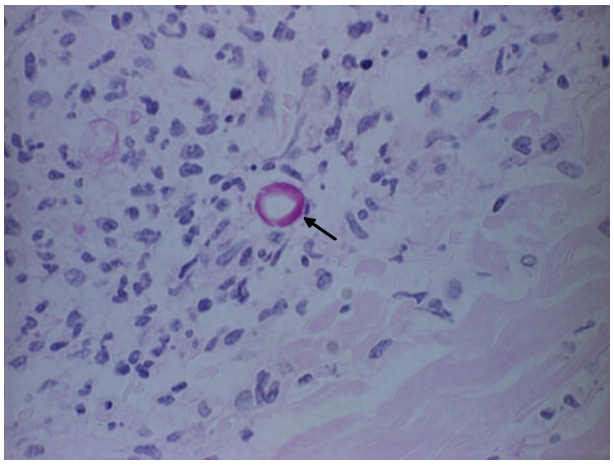


Fig 3 High power view of skin biopsy stained with periodic acid Schiff showing an ovoid structure consistent with a thick walled intercalary hyphal cell as seen in *Fusarium* spp

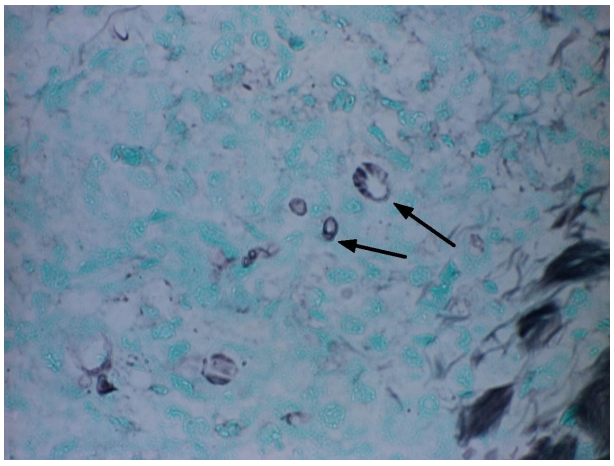


Fig 4 High power view of skin biopsy stained with Grocott's methenamine silver showing ovoid structures consistent with thick walled intercalary hyphal cells as seen in infection with *Fusarium* spp

Despite 10 days of antifungal treatment the skin lesions continued to develop, so the dose of liposomal amphotericin B

was increased (5 mg/kg) and intravenous voriconazole was added (6 mg/kg for two doses, then 4 mg/kg twice daily). In vitro sensitivity studies found that the organism was resistant to amphotericin B and had only intermediate sensitivity to voriconazole. The isolate was fully sensitive to posaconazole so antifungal treatment was switched to oral posaconazole monotherapy (200 mg four times daily) on day 22 of antifungal treatment.

He remained clinically stable with slow resolution of the skin lesions and partial resolution of the lung consolidation after six weeks of posaconazole. He was deemed unfit for bone marrow transplantation because attempted conditioning in his first remission had resulted in near cardiac arrest. Despite ongoing posaconazole treatment and 5-azacytidine chemotherapy he died of relapsed/refractory acute myeloid leukaemia four months after this episode.

Thanks to Andrew Giles, consultant histopathologist at University Hospital Lewisham, for the histopathological images.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Not commissioned; externally peer reviewed.

Patient consent obtained.

1 Dignani MC, Anaissie E. Human fusariosis. *Clin Microbiol Infect* 2004;10:67-75.
2 Nucci M, Anaissie E. Fusarium infections in immunocompromised patients. *Clin Microbiol Rev* 2007;20:695-704.
3 Boutati EI, Anaissie EJ. Fusarium, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. *Blood* 1997;90:999-1008.
4 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.
5 Sampathkumar P, Paya CV. Fusarium infection after solid-organ transplantation. *Clin Infect Dis* 2001;32:1237-40.
6 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.
7 Martino R, Subirá M, Rovira M, Solano C, Vázquez L, Sanz GF, et al. Invasive fungal infections after allogeneic peripheral blood stem cell transplantation: incidence and risk factors in 395 patients. *Br J Haematol* 2002;116:475-82.
8 Branski LK, Al-Mousawi A, Rivero H, Jeschke MG, Sanford AP, Herndon DN. Emerging infections in burns. *Surg Infect (Larchmt)* 2009;10:389-97.
9 Halpern AV, Heymann WR. Bacterial diseases. In: Bolognia JL, Jorizzo JL, Rapini RP, Callen JP, Horn TD, Mancini AJ, et al, eds. Dermatology. 2nd ed. Mosby, 2003:1075-106.
10 Leeflang MM, Debets-Ossenkopp YJ, Visser CE, Scholten RJ, Hooft L, Bijlmer HA, et al. Galactomannan detection for invasive aspergillosis in immunocompromized patients. *Cochrane Database Syst Rev* 2008;4:CD007394
11 Meersseman W, Lagrou K, Maertens J, Wilmer A, Hermans G, Vanderschueren S, et al. Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. *Am J Respir Crit Care Med* 2008;177:27-34.
12 Tortorano AM, Esposto MC, Prigitano A, Grancini A, Ossi C, Cavanna C, et al. Cross-reactivity of Fusarium spp in the Aspergillus galactomannan enzyme-linked immunosorbent assay. *J Clin Microbiol* 2012;50:1051-3.
13 Prentice AG, Glasmacher A, Hobson RP, Schey S, Barnes RA, Donnelly JP, et al. Guidelines on the management of invasive fungal infection during therapy for haematological malignancy. 2008. London, UK, British Committee for Standards in Haematology, 2008. www.bcshguidelines.com/documents/fungal_infection_bcsh_2008.pdf.
14 Maertens J, Marchetti O, Herbrecht R, Cornely OA, Flückiger U, Frêre P, et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3—2009 update. *Bone Marrow Transplant* 2011;46:709-18.
15 Slavin MA. Introduction to the updated Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting, 2008. *Intern Med J* 2008;38:457-67.
16 Agrawal S, Jones B, Barnes R, Kibbler C, Millen M, Ashcroft M, et al. A practical critique of antifungal treatment guidelines for haemato-oncologists. *Crit Rev Microbiol* 2012;38:203-16.
17 Labois A, Gray C, Lepretre S. Successful treatment of disseminated fusariosis with voriconazole in an acute lymphoblastic leukaemia patient. *Mycoses* 2011;54(suppl 4):8-11.
18 Nucci M, Anaissie EJ, Queiroz-Telles F, Martins CA, Trabasso P, Solza C, et al. Outcome predictors of 84 patients with hematologic malignancies and Fusarium infection. *Cancer* 2003;98:315-9.
19 Kontoyiannis DP, Bodey GP, Hanna H, Hachem R, Boktour M, Girgaway E, et al. Outcome determinants of fusariosis in a tertiary care cancer center: the impact of neutrophil recovery. *Leuk Lymphoma* 2004;45:139-41.

Cite this as: *BMJ* 2012;345:e8296