Case 9
A 10 year-old Thai girl from Bangkok

Chief complaint: multiple painful nodules on right arm for 6 days

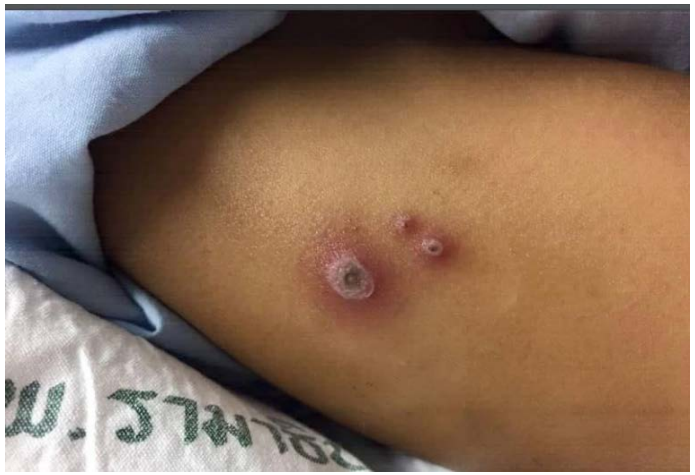

Fig. 9.1

Present illness:
The patient diagnosed with alveolar rhabdomyosarcoma with multiple lymph node metastases. She has been treated with systemic ifostamide and etoposide twenty three days prior admission. She was admitted to the hospital due to febrile neutropenia. On the third day of admission, she developed three painful erythematous nodules on her right arm under the adhesive tape near the puncture site.

Underlying disease:
Alveolar rhabdomyosarcoma with multiple lymph node metastases, treated with twelve times of radiotherapies and chemotherapies.

Physical examination:

- Vital sign: BT 41°C, BP 110/76 mmHg, P 169 bpm, RR 24/min
- GA: a Thai girl, good consciousness
- HEENT: marked pale conjunctiva, anicteric sclera, no oral thrush, no oral ulcer, intact tympanic membrane
- Lymph node: impalpable
- CVS: normal S_1S_2, no murmur
- Lung: normal breath sound, no adventitious sound
- Abdomen: soft, not tender, no hepatosplenomegaly, no perianal tenderness

Dermatologic examination: (Fig. 9.1)
Three ill-defined erythematous painful nodules with central necrosis on right arm

Histopathology: (S18-003682, skin, right arm) (Fig. 9.2, 9.3, 9.4)

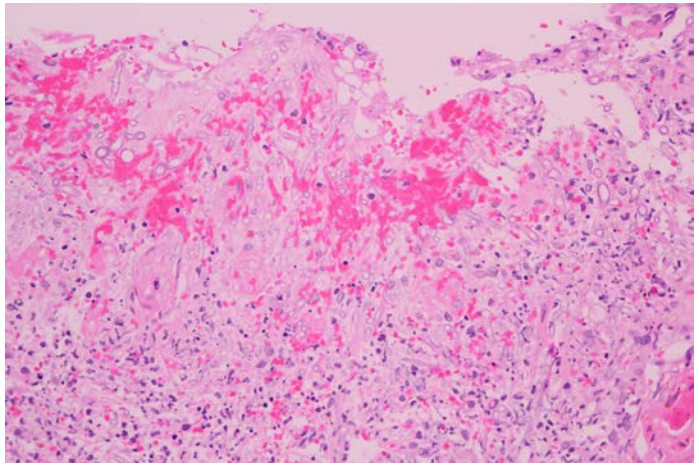

Fig. 9.2 H&E

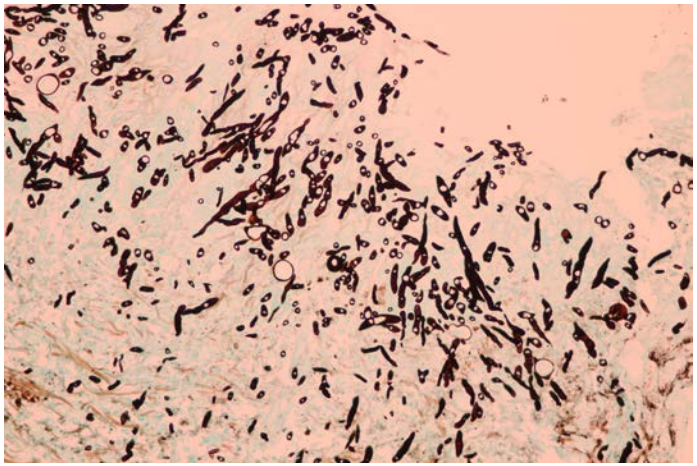

Fig. 9.3 GMS stain

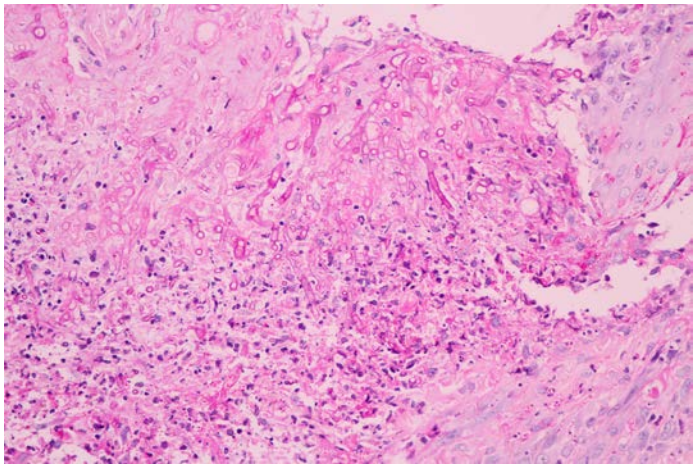

Fig. 9.4 PAS stain

- Diffuse mixed inflammatory cells infiltrate around and within necrotic ulcers
- Numerous branching septate hyphae within necrotic tissues GMS, PAS positive

Investigations:

- Tissue imprint for G/S, AFB, mAFB, GMS: all negative
- Tissue 16s gene sequencing: negative
- Tissue 18s gene sequencing: positive for *Aspergillus nomius*
- Tissue TB direct detection: negative
- Tissue culture for aerobe, and mycobacterium: negative
- Tissue culture for fungus: *Aspergillus* spp.
- CBC: Hct 18.4 %, WBC 10/cumm (too low to differentiate), Platelets 5,000/cumm MCV 82.3 fL, MCH 27.7, RDW 16.3%
- BUN 27 mg/dL, Cr 0.71 mg/dL
- LFT: ALP 135 U/L, GGT 41 U/L, AST 30 U/L, ALT 38 U/L, TP 64.6 g/L Alb 28.3 g/L, TB 0.6 mg/dL, DB 0.3 mg/dL
- Serum galactomannan: negative
- Serum cryptococal antigen: negative
- Urinalysis: WBC 0 cell/HF, RBC 0 cell/HF
- Urine culture and hemoculture: no growth
- Hemoculture for fungus: no growth
- CT chest: new, nodular-liked opacities surrounded with ground-glass opacities (Halo sign) at the RML and the RLL as well as a small nodule at the RUL suspected of invasive pulmonary aspergillosis (IPA)

Diagnosis: Cutaneous aspergillosis with invasive pulmonary aspergillosis

Treatment:

- Voriconazole 250 mg (9 mg/kg) PO bid pc 2 doses, the 200 mg (7 mg/kg) PO bid pc

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Discussion:
Aspergillosis is an opportunistic mycosis caused by fungi in the genus *Aspergillus* (A.) which are widely distributed in the environment, particularly in soil and decomposed vegetation. The most common species causing cutaneous aspergillosis are *A. flavus* and *A. fumigatus*.

Cutaneous aspergillosis is commonly divided into primary and secondary lesions. Primarily lesions accounting for direct inoculation of the fungus at the injury site and secondary lesions resulting from the blood spreading of hyphae.[1] Patients with prolonged neutropenia, allogeneic hematopoietic stem cell transplant recipients, solid organ transplant recipients, patients receiving corticosteroids, advanced acquired immunodeficiency syndrome (AIDS), and those with chronic granulomatous diseases are all increase the risk of aspergillosis. In patients with hematologic malignancies, myelodysplastic syndrome (MDS), and other diseases associated with marrow failure (e.g., aplastic anemia), the intensity and duration of neutropenia predict the risk of aspegillosis.[2, 3]

The review from Van Burik JA et al. found that the use of adhesive tape dressings was the most consistent risk factor associated with 4 from 10 cases in HIV-infected related cutaneous aspergillosis[1] as well as in Hunt SJ et al. reported two men with the acquired immunodeficiency syndrome developed foci of primary cutaneous aspergillosis beneath adhesive tape near central venous catheter sites.[4] Intermittent tape stripping of the stratum corneum of the skin with dressing changes likely caused sufficient mechanical trauma that predisposed the patients to this infection, although trapping of Aspergillus spores under the adhesive dressing could have played a role.[1]

The initial lesions of cutaneous aspergillosis may appear as macules, papules, nodules, or plaques. From the multicenter retrospective review of fifteen cases of cutaneous aspergillosis in France, most of the patients presented with nodule (6/15, 40%) followed by ecthyma-liked lesion (6/15, 20%), and inflammatory pyronychia (2/15, 13%). While pustules, cellulitis-liked lesion or ulcerative plaque were also reported.[5]

As cutaneous lesions may reflect disseminated infection, Infectious Diseases Society of America (IDSA) guidelines for management of aspergillosis 2016 recommend to treatment all the patients with cutaneous aspergillosis with systemic antifungal therapy with voriconazole in addition to evaluation for a primary focus of infection.[6] Skin biopsy should be taken from the center of the lesion and reach the subcutaneous fat to confirmation of mycological diagnosis and to visualize hyphae invading blood vessels of the dermis and subcutaneous tissues.[1] Systemic antifungal agents is the mainstay of treatment. The choices of antifungal agents are amphoptericin B, echinocandins, triazoles (e.g. itraconazole, voroconazole, posaconazole and isavuconazole). The recommended minimum duration of antifungal treatment is 6–12 weeks, largely dependent on the degree and duration of immunosuppression, site of disease, and evidence of disease improvement.[9]Surgical intervention for primary cutaneous aspergillosis may be a useful adjuct treatment to systemic antifungal therapy.[6]

Our patient presented with cutaneous aspergillosis concomitant with invasive pulmonary aspergillosis. Two weeks after received antifungal treatment, all of cutaneous lesions subsided. However, the patient passed away due to sepsis.

Reference:

1. Van Burik JA, Colven R, Spach DH. Cutaneous aspergillosis. J Clin Microbiol. 1998;36:3115-21.
2. Weinberger M, Elattar I, Marshall D, Steinberg SM, Redner RL, Young NS et al. Patterns of infection in patients with aplastic anemia and the emergence of Aspergillus as a major cause of death. Medicine (Baltimore). 1992;71:24-43.
3. Gerson SL, Talbot GH, Hurwitz S, Strom BL, Lusk EJ, Cassileth PA. Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med. 1984;100:345-51.
4. Hunt SJ, Nagi C, Gross KG, Wong DS, Mathews WC. Primary cutaneous aspergillosis near central venous catheters in patients with the acquired immunodeficiency syndrome. Arch Dermatol. 1992;1289:1229-32.
5. Bernardeschi C, Foulet F, Ingen-Housz-Oro S, Ortonne N, Sitbon K, Quereux G, et al. Cutaneous Invasive Aspergillosis: Retrospective Multicenter Study of the French Invasive-Aspergillosis Registry and Literature Review. Medicine (Baltimore). 2015;94:1018.
6. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63:1-60.