

Case 18

A 38 year-old Thai man from Samutprakan

Chief complaint: Multiple discrete indurated erythematous to purplish dermal papules on trunk and extremities for one year



Present illness:

The patient developed productive cough for 3 months with low grade fever and significant weight loss of 10 kilograms, so he went to visit a pulmonologist and chest film revealed bilateral diffuse reticulonodular infiltration. Further investigations were performed e.g. anti-HIV, blood culture for aerobe. A few days later, the blood culture was detected both budding yeasts and gram positive cocci in chain. His positive serology for HIV was definitely confirmed.

Suddenly, he was called for emergency treatment. Numerous encapsulated budding yeasts were also found in his cerebrospinal fluid.

A dermatological consultation was established later to evaluate multiple discrete indurated asymptomatic erythematous to purplish dermal papules on trunk and extremities which lasted for one year without any previous treatments.

Past history:

- He has no other underlying diseases.
- He had experienced unprotected sexual intercourse 10 years ago.

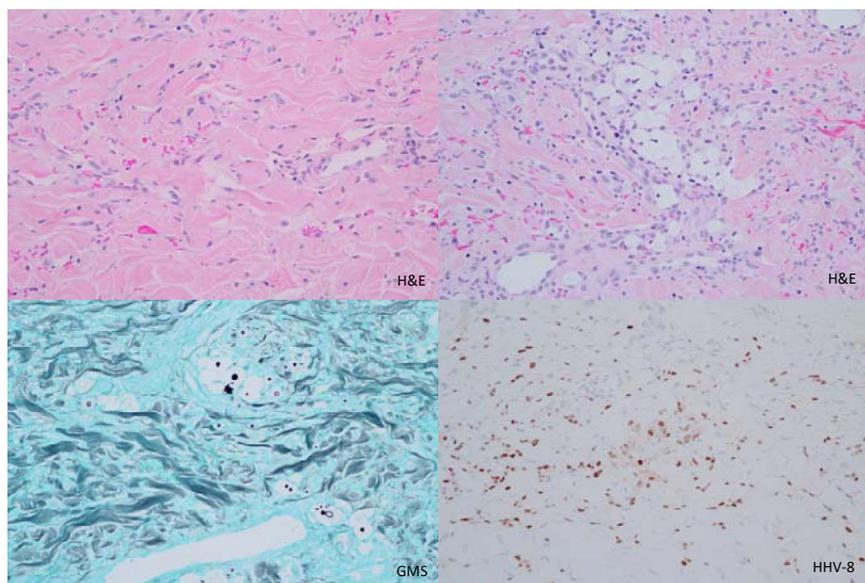
Physical examination:

V/S: T 38.6°C, P 140/min, RR 24/min, BP 134/93 mmHg
HEENT: mildly pale conjunctivae, present of oral thrush
Lymph node: no lymph node enlargement
CNS: no stiffness of neck
Other systems: unremarkable

Dermatological examination:

Multiple discrete indurated erythematous to purplish dermal papules on trunk and extremities

Histopathology (S16-16484A, Left arm)



- Perivascular and interstitial inflammatory-cell infiltration of lymphocytes and histiocytes with large vacuolated cytoplasm
- Numerous round to oval spores with thick capsules within some histiocytes
- Increased number of dilated bizarre-shaped thin-walled vessels surrounding preexisting vessels and interstitium
- Increased number of spindle cells between collagen bundles
- **Immunohistochemistry** for HHV-8: scattering positive

Investigation:

- CBC: WBC 4,190 (N 93%, L 4%, Mo 2%, Eo 1%) , Hb 10.2, Hct 31.2%, Platelet 346,000
- CD4 T cell 5% (8 cell/mm³)

- CXR: bilateral diffuse reticulonodular infiltration
- Sputum AFB: negative for 3 days
- Blood culture for aerobe: *Granulicatella adiacens*, *Cryptococcus neoformans*.
- BAL culture for aerobe: *Cryptococcus neoformans*.
- CSF culture for aerobe: *Cryptococcus neoformans*.
- BM culture for aerobe: *Cryptococcus neoformans*.
- Skin culture for aerobe: *Cryptococcus neoformans*.

Diagnosis: Kaposi sarcoma with disseminated cryptococcosis

Treatment:

- IV amphotericin B 0.7 mg/kg/day for 4 weeks then fluconazole 800 mg/day
- IV paclitaxel weekly 2 doses (cessation due to CMV colitis)
- Delayed HAART 6 weeks after treatment of cryptococcosis
- Ceftriaxone 2 gm IV OD for 14 days

Presenter: Thiraphong Mekwilaiphan, MD

Consultant: Ploysyne Rattanakaemakorn, MD

Discussion:

Kaposi sarcoma is an angioproliferative neoplasm,¹ presents as a slow growing erythematous to purplish papule, plaque, or nodule² on the skin especially on lower extremities³, the mucous membranes lining the mouth, nose, and throat, lymph nodes, or other organs e.g. lung.^{4, 5} It is different from other cancers in that lesions may begin in more than one place in the body at the same time.⁶

Those infected with HHV-8 who are most likely to develop Kaposi sarcoma have immune systems weakened by disease or by drugs given after an organ transplant⁶ as well as in this immunocompromised patient which the immunohistochemistry for

HHV-8 is scattering positive.

There are four distinct types of Kaposi sarcoma as shown in table 1.⁷

Table 1. Characteristics of Kaposi's sarcoma variants

Type	Population	Clinical	Course
Classic	Older men (50-80 years)	Usually confined to lower extremity	Usually indolent, survival 10–15 years
Endemic (African)	Young black males, 15-40 yrs, and children	Localized nodular lesions or large exophytic, aggressive lesions	Nodules indolent; aggressive lesion survival 3–5 years
Iatrogenic	Immune suppressed (e.g., renal transplant)	Localized or widespread involvement	May regress when immune suppressants discontinued
Epidemic (AIDS-related)	Primarily gay men in U.S., Europe; adults in Africa	Head, face, neck, GI and lung most common	Fulminant, survival 1-3 years without effective HIV therapy

AIDS, acquired immunodeficiency syndrome; GI, gastrointestinal system; HIV, human immunodeficiency virus.

The typical histopathology shows slit-like spaces that frequently contain red blood cells. Plasma cells and hemosiderin deposits are also usually apparent. Eosinophilic hyaline globules, 1–7 µm in size, are commonly present and form grape-like agglomerations which are predominantly intracellular. These structures are thought to represent digested erythrocytes, as the neoplastic cells seem to have phagocytic activity.⁸

For AIDS-related Kaposi sarcoma, the risk of developing Kaposi sarcoma for untreated AIDS patients is estimated to be 300 times greater than that of other immunosuppressed individuals and 20,000 times greater that of the general population⁹ as well as the more aggressive clinical course.¹⁰

Several modalities of treatment have been used for Kaposi sarcoma including chemotherapy, radiation therapy, surgical excision and Highly Active Anti-Retroviral Therapy (HAART) in patients with AIDS-related Kaposi sarcoma.¹⁴The choice of treatment is determined by the stage of Kaposi's sarcoma, its rate of progression, the degree of immune competence and HIV associated diseases.¹²

Cryptococcosis is a potentially severe infection by *Cryptococcus neoformans*. that usually occurs in a setting of

immunosuppression¹³, especially in HIV patients with a CD4 count less than 200 cells/mm³,¹⁴ mainly affects with pulmonary and resulting and/or meningeal involvements or disseminated infections.¹⁵ Clinical manifestations of cutaneous cryptococcosis are varied. Lesions may resemble molluscum contagiosum, or appear acneiform, nodular, herpeticiform, cellulitic, or keloid-like.¹⁶

The diagnostic evaluation depends on organ involvements which microbiological confirmation is required for definite diagnosis. It can easily found encapsulated unipolar budding yeasts, varying in size under light microscope. For the culture media it can grow in blood agar in aerobe culture and the appropriate culture media is Sabouraud's dextrose agar.

The current guidelines from the Infectious Diseases Society of America (IDSA) recommend treating HIV patient with at least 2 weeks of induction therapy with a combination of amphotericin B deoxycholate 0.7–1.0 mg/kg per day intravenously plus flucytosine 100 mg/kg per day orally in 4 divided doses followed by fluconazole (400 mg per day orally) for a minimum of 8 weeks and maintenance with fluconazole 200 mg per day orally life-long. Initiation of HAART should be considerably prescribed 2–10 weeks after commencement of initial antifungal treatment¹⁷ to avoid cryptococcosis-associated immune reconstitution inflammatory syndrome (C-IRIS) which is fatal condition.¹⁸

As the literature review, the coexistent Kaposi sarcoma and cutaneous cryptococcosis is rare. There were not exceed ten report cases which usually found in AIDS patients that histologically conspicuous spindle cell component for Kaposi sarcoma and small aggregates of cryptococcal yeasts. Unfortunately, half of them died during treatment.^{19, 20}

As well as this patient whose CD4 count was only 8 cells/mm³ is another one who had coexistent Kaposi sarcoma and cutaneous cryptococcosis. He was prescribed IV amphotericin B 0.7 mg/kg/day for 4 weeks then oral fluconazole 800 mg/day. Before the initiation

of HAART, the lesions on his feet became ulceration that cannot be distinguished the effect of cryptococcosis or Kaposi sarcoma, so IV paclitaxel was prescribed weekly, concurred with systemic antifungal, and discontinued due to infection of CMV colitis meanwhile HAART was then initiation 6 wks after treatment of cryptococcosis which could be effective in AIDS-related Kaposi sarcoma. Finally, the lesions were remised into post-inflammatory hyperpigmentation and the patient is still alive without recurrence in 3 following months.

References:

1. Alcantara-Reifs CM, Salido-Vallejo R, Garnacho-Saucedo GM , Velez Garcia-Nieto A. Classic Kaposi's sarcoma treated with topical 0.5% timolol gel. *Dermatol ther* 2016. doi:10.1111/dth.12381.
2. McClain CM, Haws AL, Galfione SK, Rapini RP , Hafeez Diwan A. Pyogenic Granuloma-Like Kaposi's Sarcoma. *J Cutan Pathol* 2016;43:549-51.
3. Chalya PL, Mbunda F, Rambau PF, Jaka H, Masalu N, Mirambo M et al. Kaposi's sarcoma: a 10-year experience with 248 patients at a single tertiary care hospital in Tanzania. *BMC Res Notes* 2015;8:440.
4. Suresh K, Semaan R, Arias S, Karakousis P , Lee H. Pleuropulmonary Kaposi Sarcoma in the Setting of Immune Reactivation. *J Pulm Respir Med* 2016;6. pii:352.
5. Zhang H, Wang HL, Zhong DR, Liu Y, Li NN, Zhang W et al. Fatal Pulmonary Kaposi Sarcoma in an HIV seronegative AIDS patient. *Clin Respir J* 2016. doi:10.1111/crj.12463.
6. Kaposi Sarcoma Treatment (PDQ(R)): Patient Version. PDQ Cancer Information Summaries. Bethesda (MD)2002.
7. Haverkos HW. Multifactorial etiology of Kaposi' sarcoma: a hypothesis. *J Biosci* 2008;33:643-51.
8. Kao GF, Johnson FB , Sulica VI. The nature of hyaline (eosinophilic) globules and vascular slits of Kaposi's sarcoma. *Am J Dermatopathol* 1990;12:256-67.
9. Beral V, Peterman TA, Berkelman RL , Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? *Lancet* 1990;335:123-8.
10. Voltaggio L , Montgomery E. Polypoid stromal lesions of the intestines. *Histopathology* 2015;66:88-101.
11. Krown SE. Highly active antiretroviral therapy in AIDS-associated Kaposi's sarcoma: implications for the design of therapeutic trials in patients with advanced, symptomatic Kaposi's sarcoma. *J Clin Oncol* 2004;22:399-402.
12. Martellotta F, Berretta M, Vaccher E, Schioppa O, Zanet E , Tirelli U. AIDS-related Kaposi's sarcoma: state of the art and therapeutic strategies. *Curr HIV Res* 2009;7:634-8.
13. Torres RG, Etchebehere RM, Adad SJ, Micheletti AR, Ribeiro BM, Silva LE et al. Cryptococcosis in Acquired Immunodeficiency Syndrome Patients Clinically Confirmed and/or Diagnosed at Necropsy in a Teaching Hospital in Brazil. *Am J Trop Med Hyg* 2016. pii:16-0148.
14. Bamba S, Barro-Traore F, Sawadogo E, Millogo A , Guiguemde RT. Retrospective study of cases of neuromeningeal cryptococcosis at the University Hospital of Bobo Dioulasso since accessibility to antiretroviral in Burkina Faso. *J Mycol Med* 2012;22:30-4.
15. Cazorla A, Alanio A, Bretagne S, Polivka M, Shaar-Chneker C, Kaci R et al. Cryptococcus where they are not expected: Five case reports of extra-cerebral and extra-pulmonary cryptococcosis. *Ann Pathol* 2015;35:479-85.
16. Yang Y, Shen YN, Zong WK , Cui PG. Disseminated cryptococcosis. *Indian J Dermatol Venereol Leprol* 2016;82:206-8.

17. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. *Clin Infect Dis* 2010;50:291-322.
18. Chang CC, Sorrell TC, Chen SC. Pulmonary Cryptococcosis. *Semin Respir Crit Care Med* 2015;36:681-91.
19. Pietras TA, Baum CL, Swick BL. Coexistent Kaposi sarcoma, cryptococcosis, and *Mycobacterium avium intracellulare* in a solitary cutaneous nodule in a patient with AIDS: report of a case and literature review. *J Am Acad Dermatol* 2010;62:676-80.
20. Ramdial PK, Sing Y, Subrayan S, Calonje E. Cutaneous colesional acquired immunodeficiency syndrome associated Kaposi sarcoma and cryptococcosis. *Am J Dermatopathol* 2010;32:780-6.