Case Report

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Extensive cutaneous iatrogenic Kaposi's sarcoma after bullous pemphigoid treatment with oral methylprednisolone: a rare Chinese case report

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Abstract

Bullous pemphigoid (BP) is an autoimmune disease that requires immunosuppressive therapy. Systemic corticosteroids are considered the standard treatment for moderate-to-severe BP. Kaposi's sarcoma (KS) is a rare multifocal endothelial tumour that affects the skin, mucosa and viscera. As an angioproliferative disease of obscure aetiopathogenesis and histogenesis, KS is associated with human herpesvirus 8 (HHV-8). This current case report describes a rare occurrence of extensive cutaneous KS in a 60-year-old Chinese male patient after oral methylprednisolone treatment for BP with an emphasis on its pathological characterization. A total of more than 40 nodules were found on his trunk and lower limbs covering more than 20% of his body surface area. Immunohistochemical staining of biopsy samples from the lesion showed the patient was positive for HHV-8, CD31, CD34, XIIIa, ERG and Ki-67. The Epstein–Barr virus test showed the patient tested negative for immunoglobulin (Ig)A and IgM, but was positive for IgG. Immunosuppression associated with the treatment for BP may activate a latent HHV-8 infection and induce the development of KS.

Keywords

Bullous pemphigoid, Kaposi's sarcoma, human herpesvirus 8, case report

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Introduction

Kaposi's sarcoma (KS) is a rare multifocal endothelial tumour that affects the skin, mucosa and viscera.[1] As an angioproliferative disease with obscure aetiopathogenesis and histogenesis, KS is associated with human herpesvirus 8 (HHV-8).[2] KS is mainly diagnosed in elderly Ashkenazi Jewish or Mediterranean men[3,4] and is extremely rare in China.[5] Immunocompromised patients, including those undergoing immunosuppressive therapy for bullous diseases, have a higher risk for developing KS.[6] KS is classified into four types based on the clinical circumstances in which it develops: classic (originally described by Kaposi, which typically presents in middle or old age); endemic (described in young adult males in sub-Saharan indigenous Africans and can be more aggressive); iatrogenic (associated with immunosuppressive drug therapy); and epidemic KS (acquired immunodeficiency syndrome-associated).[7] This case report describes a rare occurrence of KS in a male patient treated with methylprednisolone for generalized bullous pemphigoid (BP).

Case report

A 60-year-old male patient visited the outpatient department at Huashan Hospital, Fudan University, Shanghai, China in March 2018 with a 10-month history of generalized BP (Figure 1). He was treated

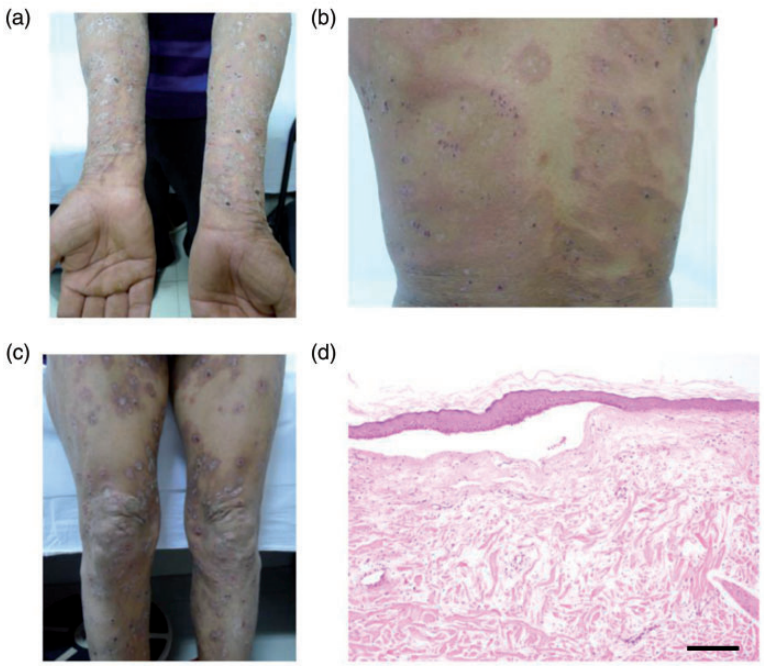

Figure 1. The clinical features of bullous pemphigoid on the forearms, trunk and legs of a 60-year-old male patient during remission (a, b and c). Haematoxylin and eosin staining of a skin biopsy confirmed a diagnosis of bullous pemphigoid (d); scale bar 50 μm. The colour version of this figure is available at: http://imr.sagepub.com.

with methylprednisolone for 7 months (highest dose 60 mg/day orally once daily for 2 weeks, gradually decreased to 22 mg/day orally once daily for 3 weeks). In October 2018, the patient developed erythaema and nodules on the trunk and all extremities. His treatment with 22 mg/day methylprednisolone orally once daily was continued. A history of drug addiction, alcohol consumption and smoking was denied. Physical examination revealed multiple (more than 40), discrete, hyperkeratotic, excoriated papules and nodules (~0.5–2 cm in diameter). These were on his trunk (about 10), neck and the extensor surfaces of his limbs (lower limbs about 30) covering about 20% of his body surface area (Figures 2a–2c). No other abnormalities were found on clinical examination, including chest and abdominal computed tomography imaging. Laboratory tests revealed that the patient tested negative for human immunodeficiency virus (HIV), the rapid plasma reagin test and treponema pallidum particle agglutination assay. Other routine tests revealed normal findings. There were no signs of a tumour. A biopsy was taken from a lesion on his right lower limb and the tissue specimen was stained with haematoxylin and eosin (Figures 2d–2f) and subjected to immunohistochemical analysis (Figure 3) for CD31(+), CD34(+), HHV-8 (+), XIIIa(+), ERG(+) and Ki-67(+). The Epstein–Barr virus test showed that the patient tested negative for immunoglobulin (Ig)A and IgM, but was positive for IgG. The patient was diagnosed with iatrogenic KS and BP. No treatment was administered because the patient requested to be discharged and went back to his local hospital. The patient was lost to follow-up.

Written informed consent was obtained from the patient's guardians for publication of this case report and the accompanying images. The study was approved for publication by the Ethics Committee of Huashan

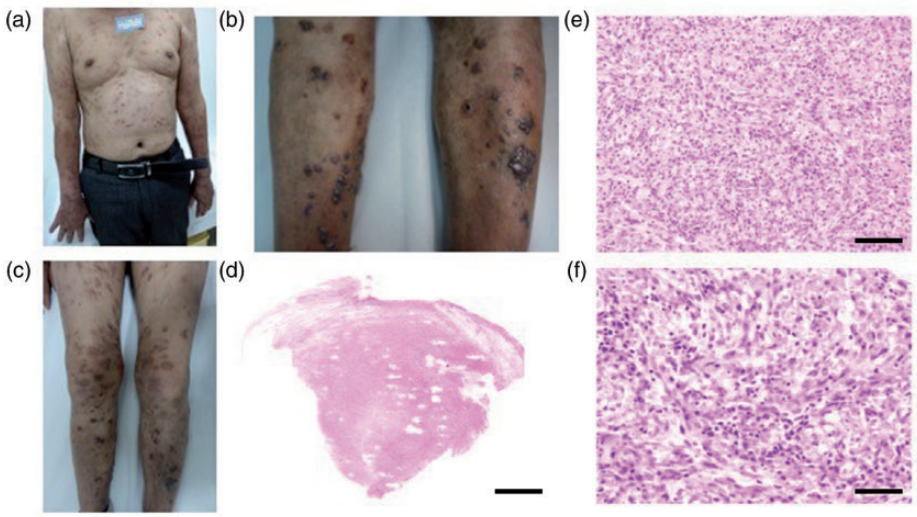

Figure 2. Multiple discrete papules and nodules were observed on the trunk and limbs of a 60-year-old male patient. Some bullae developed on normal-appearing skin or papular/nodular lesions (a–c). Haematoxylin and eosin staining of a biopsy of a Kaposi's sarcoma lesion showed hyperkeratosis, acanthosis, irregular elongation of rete ridges and subepidermal cavities; scale bar 100 μm (d); scale bar 50 μm (e); and scale bar 10 μm (f). The colour version of this figure is available at: http://imr.sagepub.com.

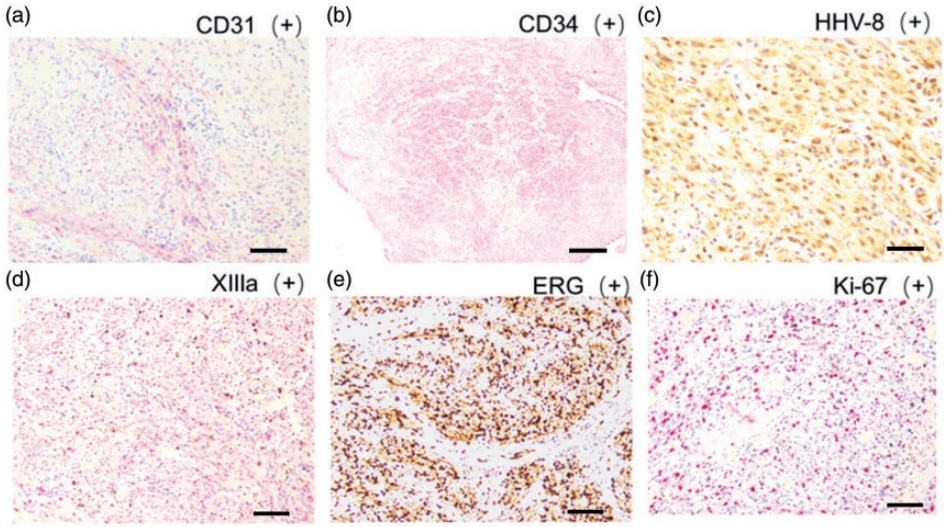

Figure 3. Immunohistochemical analysis of a biopsy of a Kaposi's sarcoma lesion for CD31, CD34, human herpesvirus 8 (HHV-8), XIIIa, ERG and Ki-67. Scale bar 50 μm. The colour version of this figure is available at: http://imr.sagepub.com.

Hospital (no. KY2018-457). Written Informed consent was obtained from the patient for treatment.

Discussion

Bullous pemphigoid is an autoimmune bullous disease that requires immunosuppressive therapy.[8] The pathogenesis of BP is attributed to autoantibodies directed against distinct adhesion molecules of the epidermis or the dermoepidermal junction.[9] Patients with BP usually present with large, fluid-filled blisters on flexural areas of the skin.[9] Pharmacotherapy for BP, which includes corticosteroid medications such as prednisone and other drugs that suppress the immune system, helps heal the blisters and alleviates itching.[9] However, BP can be life-threatening, especially for elderly individuals in poor health.[10] Only a few cases of KS associated with immunosuppressive therapy for dermatological diseases have been reported in the literature.[11–18] Due to the low incidence of these diseases, there is a lack of retrospective studies in the Chinese population on the frequency of KS in the patients with bullous diseases. Interestingly, the occurrence of classic KS in the Xinjiang Uygur Autonomous Region, the northwest part of China, is high probably due to the population being composed of 59.43% minority ethnic groups.[5] According to *HLA-B* gene analysis, some of these people originated in Europe 3000 years ago, migrated to Central Asia and Xinjiang, where they then merged with the local ethnic groups and evolved into the current race.[19,20]

Kaposi's sarcoma is caused by HHV-8 infection, which is considered to be a triggering factor for bullous diseases, especially pemphigus.[21,22] However, the association between HHV-8 and BP remains controversial.[23] A recent retrospective study in non-HIV KS patients reported that 14 (1.03%) of 1362 patients with classic or iatrogenic KS also suffered from bullous disease.[24] Half of these 14 patients developed KS after the onset of bullous disease, whereas the other half developed a bullous disease

after being diagnosed with KS.[24] Only a few cases on concurrent HHV-8 and BP have been reported in the literature.[12,21,22] HHV-8 identification in KS with BP has been reported only in one patient in the Chinese population.[25]

There are discrepancies pertaining to HHV-8 positivity in patients with KS-associated BP.[12,14] In 2001, a report of a case of KS after immunosuppressive therapy for BP demonstrated that serum HHV-8 protein was detectable 4 months before the appearance of KS and initiation of prednisolone therapy.[11] The findings in this previous case suggested that the immunosuppression associated with the treatment for BP possibly activated a latent HHV-8 infection and induced the development of KS.[11] The current patient tested positive for HHV-8 on a biopsy of the lesion. The experience with this current patient suggests that HHV-8 positivity may be an indicator for potential development of KS in BP patients. However, it is not clear whether HHV-8 induced BP and subsequently KS. To clarify the sequence and causation, it is necessary to compare the incidence of HHV-8-positive and HHV-8-negative KS appearing after the onset of BP.

Prednisolone and azathioprine are the drugs most frequently implicated in immunosuppression-associated KS.[15] It is difficult to evaluate the relationship between the type, dosage and duration of immunosuppressive medication and the onset of KS. The mean time to KS onset, according to the current literature, is 4 months from the initiation immunosuppressive therapy.[26] In this current patient, BP treatment had been administered for 7 months before the onset of KS.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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References

1. Pantanowitz L and Dezube BJ. Kaposi sarcoma in unusual locations. *BMC Cancer* 2008; 8: 190.
2. Mesri EA, Cesarman E and Boshoff C. Kaposi's sarcoma and its associated herpesvirus. *Nat Rev Cancer* 2010; 10: 707–719.
3. Schwartz RA. Kaposi's sarcoma: advances and perspectives. *J Am Acad Dermatol* 1996; 34: 804–814.
4. Fife K and Bower M. Recent insights into the pathogenesis of Kaposi's sarcoma. *Br J Cancer* 1996; 73: 1317–1322.
5. Wu XJ, Pu XM, Kang XJ, et al. One hundred and five Kaposi sarcoma patients: a clinical study in Xinjiang, Northwest of China. *J Eur Acad Dermatol Venereol* 2014; 28: 1545–1552.
6. Schulz TF and Cesarman E. Kaposi Sarcoma-associated Herpesvirus: mechanisms of oncogenesis. *Curr Opin Virol* 2015; 14: 116–128.
7. Antman K and Chang Y. Kaposi's sarcoma. *N Engl J Med* 2000; 342: 1027–1038.
8. Meurer M. Immunosuppressive therapy for autoimmune bullous diseases. *Clin Dermatol* 2012; 30: 78–83.
9. Hammers CM and Stanley JR. Mechanisms of Disease: Pemphigus and Bullous Pemphigoid. *Annu Rev Pathol* 2016; 11: 175–197.
10. Langan SM, Smeeth L, Hubbard R, et al. Bullous pemphigoid and pemphigus vulgaris–incidence and mortality in the UK: population based cohort study. *BMJ* 2008; 337: a180.
11. Sato-Matsumura KC, Matsumura T, Nabeshima M, et al. Serological and immunohistochemical detection of human herpesvirus 8 in Kaposi's sarcoma after

immunosuppressive therapy for bullous pemphigoid. *Br J Dermatol* 2001; 145: 633–637.
12. Gaspari AA, Marchese S, Powell D, et al. Identification of HHV-8 DNA in the skin lesions of Kaposi's sarcoma in an immunosuppressed patient with bullous pemphigoid. *J Am Acad Dermatol* 1997; 37: 843–847.
13. Moore PS and Chang Y. Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and those without HIV infection. *N Engl J Med* 1995; 332: 1181–1185.
14. Gao XH, Lin J, Yang C, et al. A case of Kaposi's sarcoma associated with pemphigoid nodularis. *J Dermatol* 2001; 28: 388–392.
15. Cheng TY, Hsiao CH and Chu CY. Generalized immunosuppression-associated type Kaposi's sarcoma in a patient with severe refractory bullous pemphigoid. *Dermatol Sinica* 2008; 26: 85–92.
16. Kaplan RP, Israel SR and Ahmed AR. Pemphigus and Kaposi's sarcoma. *J Dermatol Surg Oncol* 1989; 15: 1116–1121.
17. Halpern SM, Parslew R, Cerio R, et al. Kaposi's sarcoma associated with immunosuppression for bullous pemphigoid. *Br J Dermatol* 1997; 137: 140–143.
18. Scaparro E, Borghi S and Rebora A. Kaposi's sarcoma after immunosuppressive therapy for bullous pemphigoid. *Dermatologica* 1984; 169: 156–159.
19. Zhang HG, Chen YF, Ding M, et al. Dermatoglyphics from all Chinese ethnic groups reveal geographic patterning. *PLoS One* 2010; 5: e8783.
20. Zhang XN, Liu YG, Li D, et al. Polymorphism of HLADQA1, -DQB1 genes in Uygur and Kazak ethnic groups and comprehensive analysis of 25 related populations. *Yi Chuan Xue Bao* 1998; 25: 193–198 [Article in Chinese, English abstract].
21. Meibodi NT, Nahidi Y, Mahmoudi M, et al. Evaluation of coexistence of the Human Herpesvirus type 8 (HHV-8) infection and pemphigus. *Int J Dermatol* 2010; 49: 780–783.
22. Wang GQ, Xu H, Wang YK, et al. Higher prevalence of human herpesvirus 8 DNA sequence and specific IgG antibodies in patients with pemphigus in China. *J Am Acad Dermatol* 2005; 52: 460–467.
23. Galan A, Hui P and McNiff JM. Absence of human herpesvirus 8 in pemphigus and bullous pemphigoid. *Int J Clin Exp Pathol* 2009; 2: 456–462.
24. Tourlaki A, Genovese G, Guanziroli E, et al. Autoimmune bullous diseases in non-HIV Kaposi's sarcoma: a retrospective study in a large cohort of patients. *J Eur Acad Dermatol Venereol* 2018; 32: 1777–1783.
25. Wang T, Li C, Yang C, et al. Identification of human herpesvirus-8 in Kaposi's sarcoma with bullous pemphigoid. *Chin Med J (Engl)* 2014; 127: 786–788.
26. Louthrenoo W, Kasitanon N, Mahanuphab P, et al. Kaposi's sarcoma in rheumatic diseases. *Semin Arthritis Rheum* 2003; 32: 326–333.