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Case Report

Cutaneous cytomegalovirus manifestation in a HIV-negative patient

人類免疫缺陷病病毒陰性患者皮膚巨細胞病毒感染的表現

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Cytomegalovirus (CMV) is a DNA virus belonging to the herpesvirus family. They replicate in the nucleus and form intranuclear inclusions and lead to giant cell formation. They have the ability to cause latent infection in humans. Reactivation from latency might occur in immunocompromised patients. It causes encephalitis, pneumonitis, colitis, retinitis and also congenital foetal infection. Cutaneous manifestation of CMV infection, which is uncommonly reported, may present with a wide variety of skin lesions such as ulcers, erosions, erythematous morbilliform rashes, vesiculobullous diseases and sometimes Gianotti-Crosti syndrome. In view of the variety of lesions caused by CMV, the clinician should have a high index of suspicion especially in the high-risk patients. We report a Chinese female with infiltrative lung disease complicated by disseminated CMV infection with cutaneous manifestation confirmed by skin biopsy.

巨細胞病毒是脱氧核糖核酸病毒，屬於一種疱疹病毒。巨細胞病毒於細胞核內複製，形成核內包涵體及巨細胞。巨細胞病毒能於人體引起潛伏感染。病情由潛伏而出現活躍可見於免疫受損患者，可引起腦炎、肺炎、結腸炎，視網膜炎及先天性胎兒感染，巨細胞病毒感染的皮膚表現不常有報導，可表現為多種類型的皮疹，如潰瘍、糜爛、紅色麻疹樣疹、大疱類疾病及偶然有小兒丘疹性肢端皮炎。由於皮疹的多樣化，臨床醫生應對此症提高警覺，尤其是高危患者。本文報告一例華裔女性患浸潤性肺疾病併發彌散性巨細胞病毒感染及其皮膚症狀，並經由皮膚切片活檢証實。

Keywords: Cytomegalovirus, immunosuppression, intranuclear inclusion

關鍵詞：巨細胞病毒，免疫抑制，核內包涵體

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Introduction

Cytomegalovirus (CMV) belongs to the herpesvirus family. All herpesviruses have similar structures and constitute an extensive family of DNA viruses. They replicate in the nucleus and form intranuclear inclusions and lead to giant cell formation. They have the ability to cause latent infection in normal human hosts who are often asymptomatic. However, when the patients acquire an immunosuppressive state such as that in acquired immunodeficiency syndrome (AIDS) or in the recipients of bone-marrow or solid organ transplants who are taking immunosuppressive agents, the cell-mediated immunity is decreased and the virus might reactivate to cause CMV diseases. The patients may present with fever, general malaise and occasionally lymphocytosis with atypical lymphocytes. CMV also causes widespread systemic infection particularly in immunocompromised patients with attendant high mortality. It can cause encephalitis, pneumonitis, colitis, retinitis and even congenital foetal infection through trans-placental transmission. However, cutaneous manifestation of CMV infection is only uncommonly reported. It may present with ulcers, erosions, erythematous morbilliform rashes and even vesiculobullous diseases. We are reporting a Chinese female with infiltrated lung disease, who was given prednisolone and azathioprine, developing disseminated CMV infection with cutaneous manifestation.

Case report

A 58-year-old Chinese female with a history of diabetes mellitus, hypertension and left lower limb deep vein thrombosis on warfarin was followed up regularly by internists. She also had a right adnexal mass for which work-up was done by the gynaecologist. After undergoing an open lung biopsy for infiltrated lung disease in April 2007, she was provisionally diagnosed to have sarcoidosis. She was then put on prednisolone and, subsequently, azathioprine was added. After she was admitted to gynaecology ward because of the right adnexal mass and elevated CA 125 level in late September 2007, she developed fever, general malaise and shortness of breath. Physical examination revealed crepitations on auscultation. No lymphadenopathy was identified. Chest X-ray showed increased lung infiltration. As erythematous plaques with erosions were found on the face (Figure 1), upper chest wall and left breast and areolar region (Figure 2),

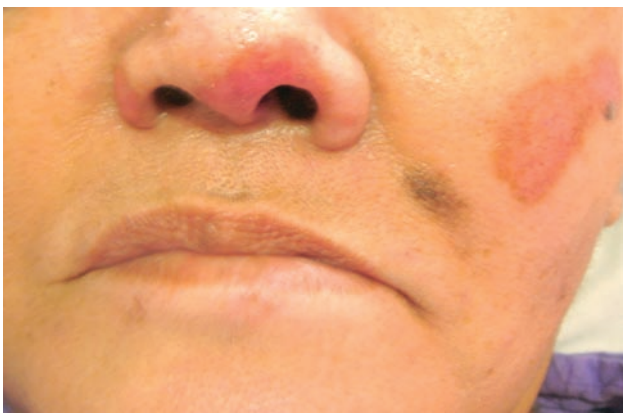

Figure 1. Erythematous erosive plaque on the left cheek.

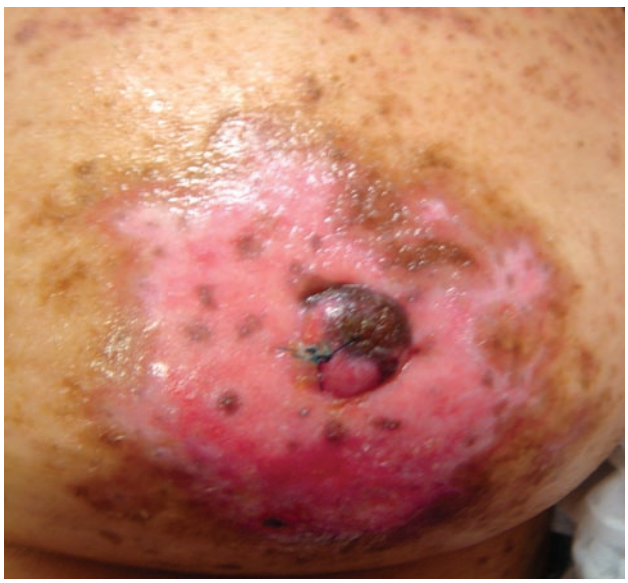

Figure 2. Erythematous erosive plaque on the left breast involving the nipple and aerolar region.

she was transferred to the medical unit for further management.

Viral culture on the erosions of the face was positive for herpes simplex virus type 1. Skin biopsy on the left breast erythematous erosive plaque was performed. The biopsy showed extensive erosion and the epidermis was covered by crust while the underlying epidermis had intercellular oedema. There was basal keratinocytic atypia consistent with reactive atypia. There was no pagetoid cell infiltration. The deeper section showed cytomegalic inclusions in scattered fibroblastic cells and endothelial cells (Figure 3). Immunohistochemical staining confirmed the presence of cytomegalovirus. Hence, the skin biopsy confirmed the presence of cutaneous CMV infection. Other investigations in this patient suggested that the CMV infection was disseminated. Features suggestive of CMV retinitis were found by the ophthalmologist. Transbronchial biopsy via flexible bronchoscopy showed lung tissue with mild mixed inflammatory cell infiltration. Ziehl-Neelsen stain for acid-fast bacilli was negative but Grocott stain showed some cup-and-saucer shaped fungal organisms in the exudates which were compatible with pneumocystitis carinii (PCP) species morphologically. Although granuloma and viral inclusion were not obvious, immunohistochemical study for cytomegalovirus showed positivity. Thus, she was suffering from PCP and CMV pneumonitis. Furthermore, CMV colitis was confirmed by colonoscopy. Multiple ulcers were found over caecum, ascending colon, sigmoid colon and rectum. Histology showed chronic inflammatory infiltrate. Granuloma formation was identified on the colonic mucosa. Ziehl-Neelsen stain was negative for acid-fast bacilli and there was no evidence of dysplasia or malignancy. Immunohistochemical stain was also positive for cytomegalovirus. The CMV pp65 antigenaemia was positive (42 / 2 x 10^5 WBC) which indicated that she was having active CMV infection. Human immunodeficiency virus (HIV) 1 and 2 antibodies were negative. Hence, this lady with an immunocompromised state due to systemic steroid and immunosuppressive agents given for her infiltrative lung disease suffered from disseminated CMV infection resulting in retinitis, pneumonitis, colitis and multiple cutaneous ulcerated plaques. The patient was then given ganciclovir 5 mg/kg intravenously every 12 hours for a total duration of three weeks. Subsequently, the CMV pp65 antigenaemia turned negative.

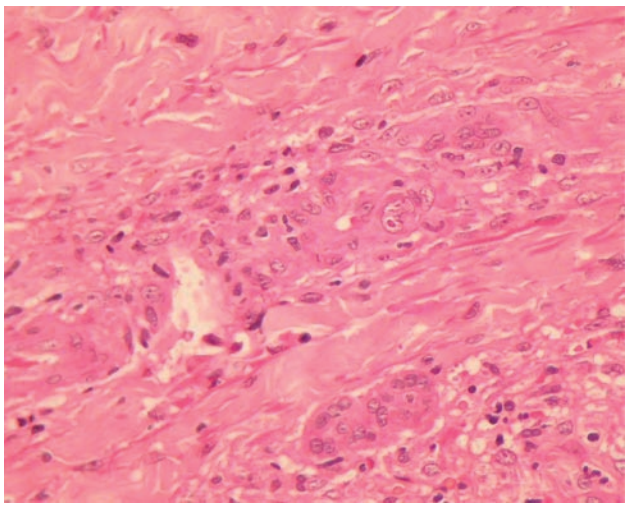

Figure 3. Skin biopsy revealing intranuclear inclusion. (H&E, Original magnification x 400)

Discussion

CMV belongs to the family of herpesvirus which infects most of the population. After the initial infection, it enters into a latent phase and becomes asymptomatic in most people with normal immunological status. CMV can however cause diseases involving multiple organ systems in those immunocompromised hosts. Encephalitis, pneumonitis, colitis and retinitis are the more well known CMV diseases that are potentially fatal. CMV infection has become one of the more serious diseases in the heavily immunosuppressed patients such as those with HIV/AIDS and very low CD4 count and organ-transplant recipients

receiving high dose of immunosuppressants. It has been estimated that in renal transplant recipients, 20% of graft failures, 30% of febrile episodes and 25% of deaths are caused by CMV.[1] However, cutaneous manifestation of CMV disease is rarely reported even in the high-risk group. It is because CMV disease of the integument is not clinically distinctive enough to alert the attending clinician for the condition. The presentation includes erosions, ulcers, macules, papules and even morbilliform eruptions.[2]

Erosion and ulcer seem to be more commonly reported in the literature. Horn and Hood[3] reported five immunosuppressed patients with CMV skin infection presented with perineal ulcers which were all confirmed by skin biopsies. Two of them had AIDS, two were the recipients of renal transplants and one had rheumatoid arthritis who was put on systemic steroid. Three of them also had concomitant herpes simplex virus (HSV) infection confirmed by positive herpes culture. Similarly, our patient had a positive HSV culture from the facial erosion and confirmed CMV infection from the skin biopsy. The authors postulated that CMV did not cause the ulcer. HSV might be the initiating agent producing the ulcer and then CMV might reside in the granulation tissue in the ulcer base. Hancox et al[4] reported a case of CMV with perineal papules, erosions and ulcers in a preterm baby who was presumably immunocompetent. The mode of transmission was unclear and there was no extra-perineal CMV involvement. The lesions resolved without any CMV-specific therapy and there were no obvious physical sequelae. Moreover, large painful ulceration may also be one of the features of CMV cutaneous manifestations. A middle aged woman with systemic lupus erythematosus (SLE) on prednisolone developed multiple tender ulcerations, largest being 8 x 15 cm, with marked undermining of the ulcer borders, thick black central eschars and a purulent exduate. Subsequent skin biopsy showed cytoplasmic inclusions and the immunoperoxidase staining was positive for CMV.[5] Another author also reported a liver transplant patient who had cutaneous CMV disease presented with multiple necrotic ulcers over the chest, upper arms and thighs.[6]

CMV cutaneous infection may also present as macular and papular eruptions. A 58-year-old chronic renal insufficiency patient developed erythematous scaly macules and papules on the lower limbs with progressive upward extension to buttock. Skin biopsy showed CMV infection with characteristic intranuclear inclusions (owl's eye).[7] Another renal transplant recipient developed erythematous papular rash, non-pruritic and non-confluent, distributed over the trunk. The skin biopsy was consistent with CMV infection disclosing cytomegalic cells with intranuclear inclusions.[8] Lee also reported a heart-lung transplant patient who developed a generalised erythematous and purpuric morbilliform eruption. The initial presumptive diagnosis was drug eruption or leucocytoclastic vasculitis. Nonetheless, the skin biopsy revealed cytomegalic inclusion compatible with CMV cutaneous infection.[9]

In addition to the aforementioned lesions, CMV cutaneous infection can also be presented with other rarer types of skin lesions. Feldman and his colleagues reported a Hodgkin's lymphoma patient developing several 2 to 3 cm tender hyperpigmented indurated plaques over the medial aspect of both thighs. It was subsequently confirmed to be CMV infection by skin biopsy.[10] Verrucous or warty lesions may also appear in CMV cutaneous infection. A patient who had AIDS presented with warty growth on a translucent firm base over right heel. Another AIDS patient developed multiple 1 to 3 cm verrucous, crusty necrotic and proliferating lesions which were surrounded by erythematous and infiltrated skin. Both were confirmed to have CMV infection by skin biopsy.[11] Vesiculobullous eruptions are well known to occur in viral infections such as smallpox, hand-foot-mouth disease and particularly the herpesvirus infection caused by herpes simplex, herpes zoster and varicella. CMV infection can

sometimes present as vesiculobullous lesions. Bhawan et al[12] reported a patient with progressive glomerulonephritis and vasculitis on high dose prednisolone (80 mg daily) and cyclophosphamide (150 mg daily) developed disseminated CMV infection with several asymptomatic vesicles and bullae on erythematous base over his extremities and scalp. Multinucleated giant cells were seen on Tzanck smear. Although no inclusions were seen in the endothelial cells under light microscopy, electron microscopy revealed intracytoplasmic and intranuclear viral particles consistent with the herpes group viral infection. Moreover, the cultures of vesicular fluid yielded CMV only. Gianotti-Crosti syndrome that is characteristically associated with underlying viral illness may be associated with CMV infection. A bone-marrow transplant patient developed numerous monomorphic 2 to 3 mm erythematous papules with pruritus bilaterally on the dorsa of hands and feet and spread symmetrically over the face, buttocks, arms and legs. Accompanying CMV antigenaemia was found. The skin biopsy showed no conspicuous cellular infiltrates invading the basement membrane that was the characteristic feature of graft-versus-host disease (GVHD). Furthermore, the skin rash subsided after ganciclovir. All these features were consistent with the diagnosis of Gianotti-Crosti syndrome. Therefore, it may be associated with CMV infection particularly taking the temporal sequence of CMV antigenaemia into consideration.[13] Table 1 summarises the different presentations of cutaneous CMV infection reported by the authors.

In summary, cutaneous CMV infection can present with a wide variety of skin lesions. More common lesions include erosions and ulcers with granulation base and there is often co-infection with herpes simplex virus. It can also present with papular and morbilliform eruptions. Rarely, it may present as a verrucous warty growth, vesiculobullous lesion and even Gianotti-Crosti syndrome. In other words, it is non-specific and not distinctive. However, CMV cutaneous infection may signify a disseminated infection with the attendant fatal outcome, especially in the immunocompromised patients. Therefore, the clinician should have a high index of suspicion of cutaneous CMV infection in high-risk patients. A skin biopsy, a relatively safe and easily accessible investigation, should be done to aid determining the possibility of disseminated CMV infection so that specific anti-viral therapy can be initiated.

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Table 1. Reported cutaneous manifestations in CMV infection

Perineal ulcer co-infected with herpes simplex virus[3]
Perineal papules[4]
Large painful ulcer with marked undermining ulcer border and thick black central eschar[5]
Multiple necrotic ulcers[6]
Macular and papular eruptions[8]
Generalised erythematous and purpuric morbilliform eruption[9]
Tender hyperpigmented indurated plaques[10]
Verrucous or warty lesions[11]
Vesiculobullous eruption[12]
Gianotti-Crosti syndrome[13]

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