Cytomegalovirus-induced vasculopathy and anogenital skin ulcers in a patient with multiple myeloma

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INTRODUCTION

Cytomegalovirus (CMV) infection is one of the most common opportunistic viral infections in patients who are immunocompromised.[1] In patients with multiple myeloma (MM), novel antimyeloma agents have improved outcomes; however, this has also led to an increase in the incidence of infections by members of the Herpesviridae family, including CMV.[2] We report a case involving anogenital skin ulcers related to CMV-induced vasculopathy in a patient with MM.

Abbreviations used:

CMV: cytomegalovirus
MM: multiple myeloma

CASE REPORT

A 63-year-old man with IgA-λ MM was being treated with lenalidomide-containing medication regimens, including daratumumab, lenalidomide, and dexamethasone therapy, for 2 years after peripheral blood stem cell transplantation therapy. Skin ulcers developed in the left inguinal region, and multiple small subcutaneous nodules developed in the inguinal, perineal, and perianal regions consecutively within 1 month.

When he was referred to our department, purpuric change of the skin was also observed around multiple ulcers and nodules. The skin over the painful subcutaneous nodules became necrotic and ulcerated (Fig 1). Varicella zoster virus antigen and herpes simplex virus 1 and 2 antigens were not detected from the ulcer.

The histologic examination of the skin and a subcutaneous nodule revealed massive extravasation of red blood cells in the superficial dermis and subcutaneous tissue. Vascular occlusion of small-sized vessels with perivascular infiltration of neutrophils (Fig 2) and CMV-related inclusion bodies were detected in the large endothelial cells (Fig 3). The presence of CMV was confirmed via immunohistochemical analysis (Fig 4). The serum CMV antigen, C7HRP, was also detected, and the patient was diagnosed with CMV-induced vasculopathy.

Ophthalmologic examination also revealed CMV retinitis. Ganciclovir treatment was initiated for 20 days, followed by suppressive therapy. The skin ulcers and subcutaneous nodules healed in 1 month, and the surrounding purpura developed pigmentation.

DISCUSSION

A hypercoagulable state often develops in patients with cancer, with higher thromboembolic risk compared with patients without cancer. Thrombosis is a known clinical complication in patients with MM, and an increased rate of venous thromboembolism has been reported after the induction of multiagent chemotherapy, including lenalidomide, which is a potent, widely used immunomodulatory drug.[3] Thromboprophylaxis is now recommended throughout the course of the disease in patients with MM.

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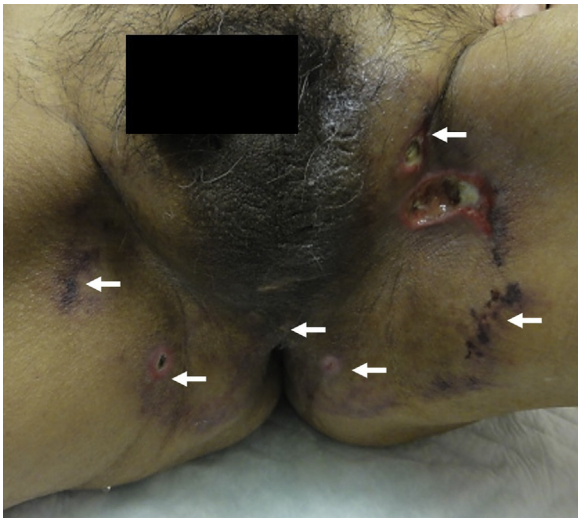

Fig 1. Skin ulcer in the left inguinal region and multiple small subcutaneous nodules (*arrows*) in the inguinal, perineal, and perianal regions. Purpuric changes of the skin were also observed around the ulcer and nodules.

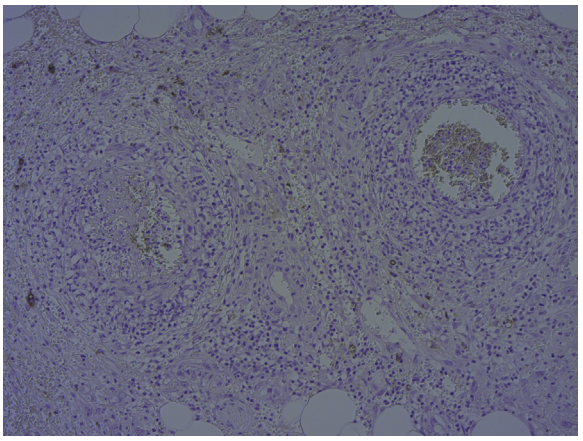

Fig 2. Histological examination of a subcutaneous nodule (hematoxylin and eosin stain; original magnification: ×200) shows vascular occlusion of small-sized vessels with perivascular infiltration of neutrophils and massive extravasation of red blood cells.

In our patient, lenalidomide was used in combination with aspirin for 2 years. The MM disease status had been stable (International Staging System: stage II), and laboratory examination results for factors involved in thrombogenic conditions, such as fibrinogen, D dimer, protein C and S, antithrombin III, and factor VIII, were within normal reference levels. The patient also tested negative for anti-cardiolipin antibody. However, because the skin manifestations rapidly resolved after ganciclovir initiation, we believe that the vascular occlusions were caused by CMV-induced vasculopathy and not MM-related or lenalidomide-related thrombosis.

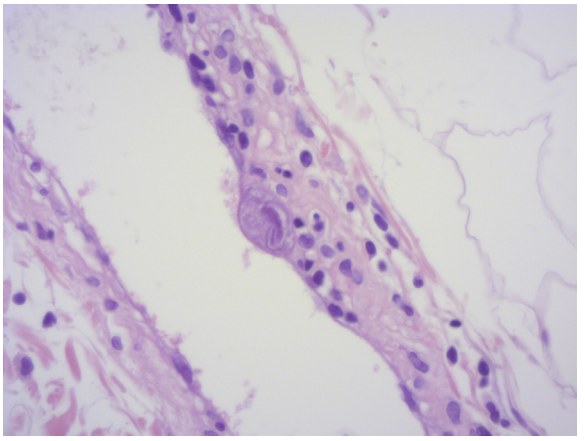

Fig 3. Cytomegalovirus-related inclusion bodies in the large endothelial cells (hematoxylin and eosin stain; original magnification: ×400).

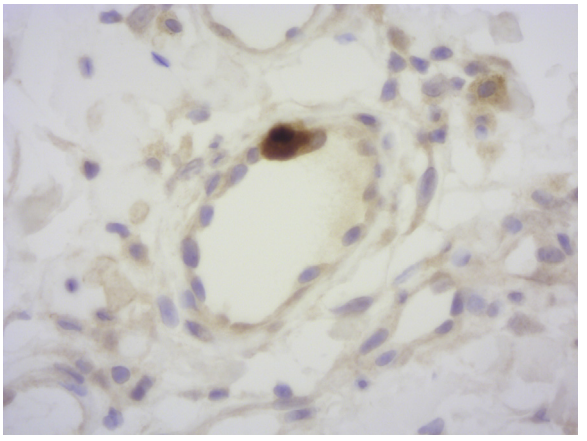

Fig 4. Positive staining of endothelial cells for cytomegalovirus pp65 antigen on immunohistochemistry (original magnification: ×400).

In patients who are immunocompromised, CMV causes various types of skin lesion. During early stages of CMV infection or its reactivation, viremia and an intraendothelial viral phase occur, which may cause rash and vasculitis. In the later stages or severe infection, cutaneous ulceration may develop.[4] There are many reports describing CMV-induced cutaneous vasculopathy and venous thrombosis.[5,6] With regard to the role of CMV in thrombogenesis, it is believed that vascular endothelial inflammation and vasculitis caused by CMV infection leads to procoagulant activity. Alternatively, the virus may acquire procoagulant properties, such as procoagulant phospholipid and tissue factor, during replication inside endothelial cells and induce thrombogenesis by upregulating thrombin production and by facilitating the activation of factor X.[6]

CMV-induced cutaneous vasculopathy is typically observed in the extremities.[6] In patients positive for HIV, skin lesions sometimes manifest as mucocutaneous ulcers in perianal lesions. Previous herpes simplex virus infection and trauma could have disrupted the skin barrier and facilitated dermal penetration of CMV into the perianal region. In these conditions, fecal shedding of the virus in the gastrointestinal tract could establish CMV perianal ulcers.[4]

The skin lesions in our patient also developed only in limited areas, such as in the inguinal, perineal, and perianal regions. However, they started as subcutaneous nodules, and skin ulcers developed secondarily. We believe that the etiology of skin ulceration in our patient was vasculopathy and thrombosis caused by CMV viremia instead of dermal penetration. We could not elucidate why CMV-induced vasculopathy occurred only around the perianal area.

Choi et al[7] reported 9 cases of cutaneous CMV infection in patients who were HIV negative and immunocompromised, patients with hematologic disease, or organ transplant recipients. In their study, 7 adult cases involved anogenital lesions (ulcerations and nodule) and 2 pediatric cases involved extragenital lesions (nodule and rash). The authors speculated that the pathogenic mechanisms for cutaneous CMV infections may have been different according to patient age.

Treatment strategies for MM have progressed; however, increased risk of infection, including CMV infection, has been reported. Nahi et al[8] showed that daratumumab also led to higher susceptibility to infections and suggested the use of antiviral and antibacterial prophylaxis. Cutaneous manifestations of CMV infection are thought to be variable, rare, and sometimes difficult to diagnose. Because delayed treatment leads to severe infection and a poor prognosis, early diagnosis of CMV infection and careful systemic screening is required.

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