Cutaneous cytomegalovirus manifestations, diagnosis, and treatment: a review

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Abstract The possible presentations of cytomegalovirus (CMV) are vast not only in its systemic manifestations, but also in the various cutaneous lesions that may result. Cutaneous cytomegalovirus is rarely reported in the literature because the clinical and pathologic features can be difficult to identify. Its identification, however, is vital as cutaneous human CMV infection can signal systemic disease and an unfavorable prognosis. The objective of this study is to aid in recognition, diagnosis, and treatment of CMV according to dermatological evidence. A complete literature search was performed within PubMed, resulting in the inclusion of 58 patient cases. The most common dermatologic manifestation was perianal or oral ulcers, but the locations and types of lesions noted throughout the review were numerous. Treatment is often simple, yet incorrect diagnoses along with concurrent illnesses can often complicate management. It is imperative for CMV to be detected early in its course to prevent mortality, especially in the immunocompromised. Dermatological presentations are often the first sign of this deadly virus' activity and it is essential that these diagnoses are made more efficient and accurate.

Keywords: cytomegalovirus, dermatology, cutaneous, diagnosis, treatment, immunodeficiency, early detection

Introduction

Human cytomegalovirus (CMV) is a highly prevalent double-stranded DNA virus in the *Herpesviridae* family. Over 60% of the population in the western world has been exposed to CMV and up to 100% in some countries of Africa and Asia [1]. Transmission occurs predominantly through saliva, as well as through the placenta, breastfeeding, sexual contact, blood transfusions, hematopoietic stem cell transplant, and organ transplants. Like all herpes viruses, CMV persists for the life of the host, establishing and maintaining latency without causing symptoms unless reactivated, most commonly during periods of immunosuppression. Thus, the prevalence of active infection has increased in past years owing to HIV infections, chemotherapy use, and the number of organ transplants performed [1]. Technological advances have allowed for greater efficacy and availability of organ transplants, but immunosuppression cannot be avoided in the process.

Although there are cases of primary infection often with symptoms of mononucleosis like-syndrome in immunocompetent patients, the majority of CMV related illnesses are related to reactivation of a latent virus. Myeloid progenitor cells and monocytes are the primary reservoir for CMV latency, where the necessary protein for transcription activation, the immediate-early (IE) promoter, remains repressed [2]. Differentiation of myeloid cells and monocytes leading to macrophages and dendritic cells allows the lytic (productive) phase of the virus to become possible [3]. Within these differentiated cells, repression of the viral IE gene expression is lifted and the viral genome can become fully activated [3]. In a

healthy carrier, the cytotoxic T-cell response clears the infected cells efficiently; in an immunocompromised host, however, the virus disseminates [3].

Systemic manifestations of CMV infection can cause a multitude of problems including pneumonitis, gastrointestinal disease, hepatitis, retinitis, and aseptic meningitis among many others [2]. Although systemic effects are more common, there are also cutaneous effects of CMV infection that can be the first sign of an unfavorable prognosis. Although cutaneous CMV is rarely reported in the literature, the actual incidence may be significantly higher, as both the clinical and pathologic features can be difficult to identify and are not pathognomonic [4]. If CMV manifests as a visible lesion and the infection is diagnosed early, then physicians have the potential to drastically reduce the morbidity and mortality of affected patients.

Methods

A PubMed search of key phrases was done with a ten-year filter from the year 2017, thus including articles from the year 2007 and after. The search terms included: [cytomegalovirus AND skin], [cytomegalovirus AND dermatology], [cytomegalovirus AND mucocutaneous], [cytomegalovirus AND ulcer], [cytomegalovirus AND oral], [cytomegalovirus AND maculopapular], [cytomegalovirus AND morbilliform], [cytomegalovirus AND petechiae], [cytomegalovirus AND purpura], [cytomegalovirus AND erosions], [cytomegalovirus AND rash]. A total of 53 case reports were included in the review in which a total of 58 patients presenting with cutaneous CMV manifestations were discussed. The presentation of the patient's lesion, diagnosis methods, treatments, and outcomes were noted for each patient.

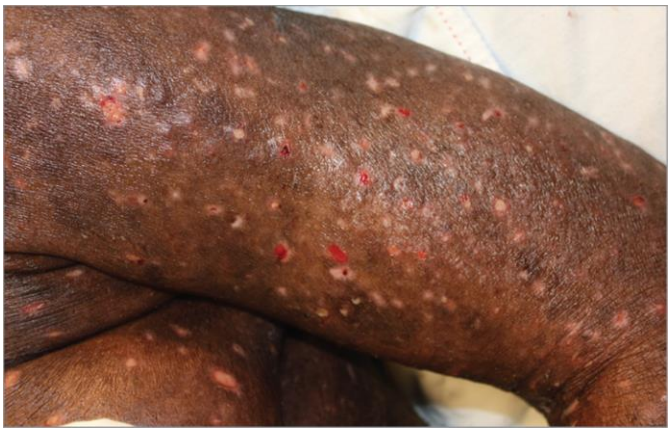

Figure 1. *Clinical photo of disseminated cutaneous CMV ulcers. Reproduced with permission from JAMA Dermatology. 2015. Volume 151 (12):1380-1381. Copyright© (2015) American Medical Association. All rights reserved.*

Discussion

Dermatological manifestations: Within the case reports reviewed, the cutaneous lesions associated with CMV were: morbilliform rash, petechiae, purpura, plaques, vesicles, bullae, erosions, erythema, nodules, papules, edema, vasculitis, and pustules. The most common of the reported cutaneous lesions were ulcers. Forty two of the 58 patients presented with ulcers, but they were not uniform in character or distribution. These ulcers varied, as some were both painful and tender or non-tender. Of the patients with ulcers, 18 had ulcers in the genital, perianal, or gluteal regions and 9 patients had oral ulcers. Other patients had ulcerative lesions in various locations at the same time and 6 had lower extremity ulcers. In **Figure 1**, shallow diffuse ulcers over the trunk and upper extremity are depicted in a patient with cutaneous CMV [5]. The locations of the ulcerative lesions among the patients are summarized in **Figure 2**. It has been thought that the preferential perianal location could relate to preferential latency of the CMV virus in the gastrointestinal tract, which can lead to fecal shedding during periods of reactivation [6].

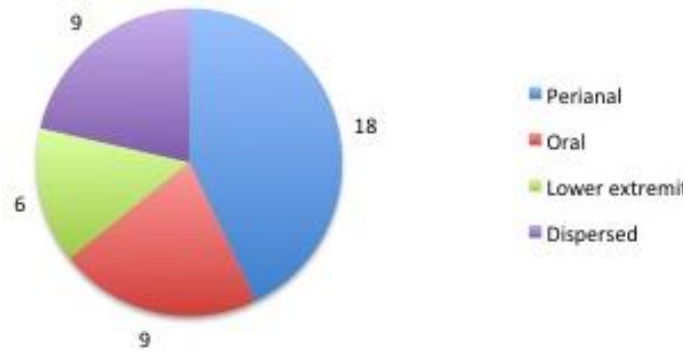

Figure 2. *Various locations of ulcer lesions in patients diagnosed with cutaneous CMV.*

Four patients within the case reports were diagnosed with CMV reactivation after drug-induced hypersensitivity syndrome (DIHS), resulting in cutaneous manifestations that only resolved when the CMV infection was targeted. The complete mechanism has not yet been discovered, but there is evidence that DIHS can cause reactivation of latent viruses, such as CMV [7]. The patient presentations varied from ulcerated erythematous plaques and papules to widespread, dark-red erythema and purpura. These are cases in which the patients were not immunocompromised before displaying CMV infection. It has been proposed that the offending drug causing the DIHS causes expansion of the regulatory T-cell population, which reactivates latent herpesviruses [7]. Tissue damage occurs as a result of activated $CD8^+$ T-cells that have targeted viral antigens [7].

Among the rarer cutaneous manifestations of CMV that appeared within the review process were pruritus, nodules, purpura, and petechiae. Three reports presented patients with purpura or a petechial rash as the only dermatological symptom. All these cases resulted in a diagnosis of secondary immune thrombocytopenic purpura (ITP) or microangiopathy related to CMV, two of which were only diagnosed after refractory treatment for primary ITP. The pathogenesis of viral induced ITP has several mechanisms, but all involve infection and immune dysregulation [8]. Aberrant formation of auto-antibodies to platelets, direct cytopathic action of the virus towards hematopoietic cells, and endothelial damage leading to vascular thrombosis are all plausible hypotheses for CMV induced thrombocytopenia causing purpura [8, 9]. Only one of the ITP patients was immunocompromised with a diagnosis of HIV and thus this patient's symptoms were likely related to reactivation, but the other two patients' thrombocytopenia appeared to be the result of a primary infection.

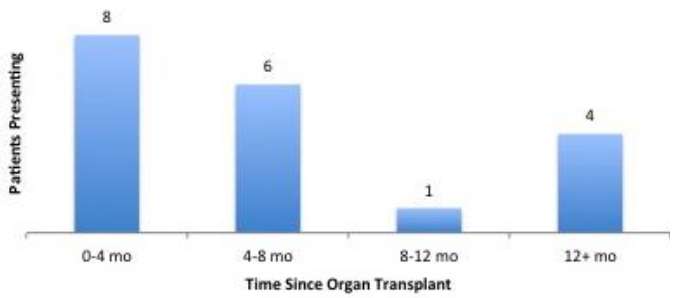

Figure 3. *Time since organ transplant at presentation.*

Diagnosis: A timely and accurate diagnosis of CMV is essential for preventing fatal outcomes and there are several methods employed in order to achieve this outcome. It is important to note that since the diagnosis is not easily made by clinical appearance, the first diagnosis is often incorrect. It is also relevant to note that several patients were presumptively treated with valacyclovir to treat herpes simplex virus (HSV) lesions, only to have a lack of results owing to concurrent CMV infection. It is not uncommon to have simultaneous HSV and CMV activation within a lesion and this occurred in ten of the reviewed patient reports. Cytomegalovirus must also be considered in the case of immunocompromised patients with skin ulcers that are not responding to antibiotic therapies. Of the total case reports, 19 documented how long after organ transplant the patient presented with cutaneous lesions; these results are summarized in **Figure 3**.

The most common method utilized for diagnosis throughout the review was skin biopsy followed by histopathological identification of intranuclear inclusions. Hematoxylin and eosin stain is employed to reveal dense inclusion bodies that can appear either in the nucleus or cytoplasm with surrounding halos as an additional unique feature. Biopsies of a lymphoma patient diagnosed with cutaneous CMV are shown in **Figures 4-6**. Microscopic examination of suspicious skin lesions is known as the most sensitive manner of cutaneous CMV diagnosis; 40 of 58 patients were diagnosed in this manner [10]. Although this was the most common approach to diagnosis, other methods were utilized in combination with the biopsy. The remaining patients within the reports did not undergo skin biopsy at all.

Only four patients were diagnosed with CMV solely by the presence of intranuclear inclusions within a skin biopsy. Other common methods included PCR, more commonly from skin biopsy but also done via serological testing. PCR quantitative analysis was

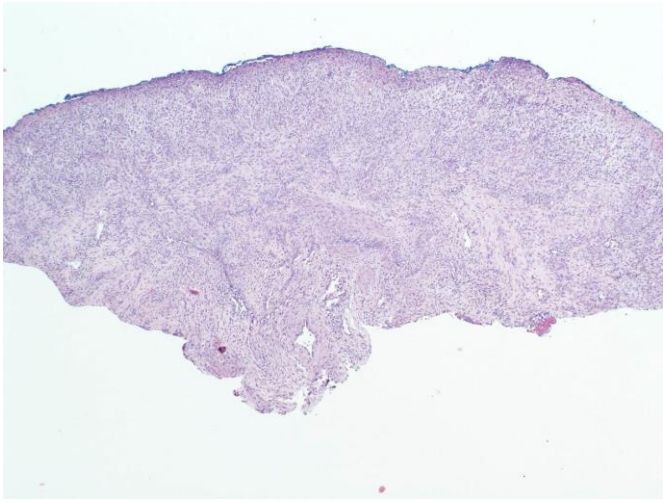

Figure 4. *Low-power magnification of the punch biopsy shows superficial and deep perivascular and interstitial mixed inflammation. H&E. 4×.*

also used to detect treatment efficacy. Eleven of the reviewed cases employed CMV antibody assays to detect infection, but also to differentiate an acute infection with an IgM positive result from a latent reactivation with positive IgG testing [11]. Another approach to patient diagnosis was a blood antigen assay, which detects CMV viral antigen pp65 with monoclonal antibodies, in which a positive result is around 200 positive cells of 200,000 leukocytes [11]. Skin biopsy with immunohistochemistry (IHC) was performed in 31 of the reviewed cases, in which antibodies were either directed towards the pp65 antigen or to CMV itself. Most diagnostic processes were directed towards the skin or to serum testing, but there were a few cases with systemic manifestations in addition to cutaneous lesions, such colonic ulcers. In these cases, biopsies were taken from the colon and physicians ordered PCR, IHC, or microscopic examination in order to reach a diagnosis.

Treatments and outcomes: The outcome of untreated CMV in an immunocompromised patient can be fatal, but when proper therapy is given, the results are often positive as evidenced throughout this review. There were a couple of unique regimens employed for treatment, but 39 of the 58 patients were only treated with the antivirals valganciclovir or ganciclovir (IV or oral). With this therapy the patients' symptoms resolved in as soon as one week to several months. Only 6 patients were continued on the antivirals for prophylaxis and one patient was prescribed daily valganciclovir for indefinite use. All these patients were either renal transplant patients or patients diagnosed with HIV. In addition, many patients were on immunosuppressive medication owing to previous organ transplant., Therefore these medications were reduced or stopped completely during treatment. Other regimens used in uncomplicated CMV cases included two instances of

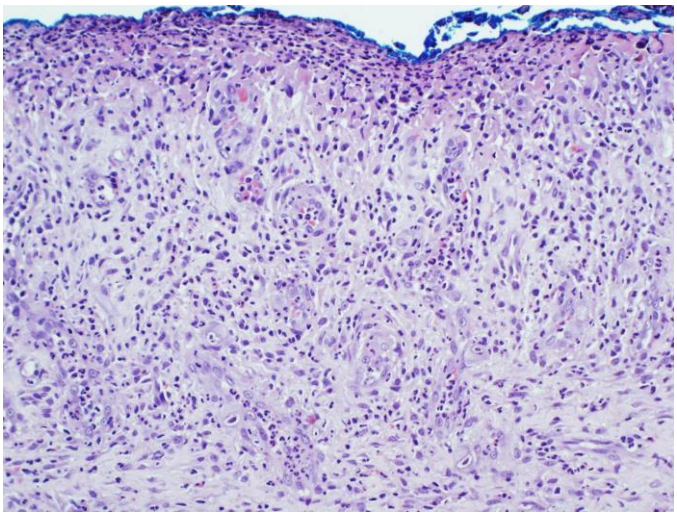

Figure 5. *On higher magnification, the interstitial inflammation predominantly consists of histiocytes and neutrophils with perivascular lymphocytic inflammation. Vasculitis is present with endothelial swelling, neutrophil infiltration of the vessel wall, and surrounding fibrinoid degeneration. H&E, 20×.*

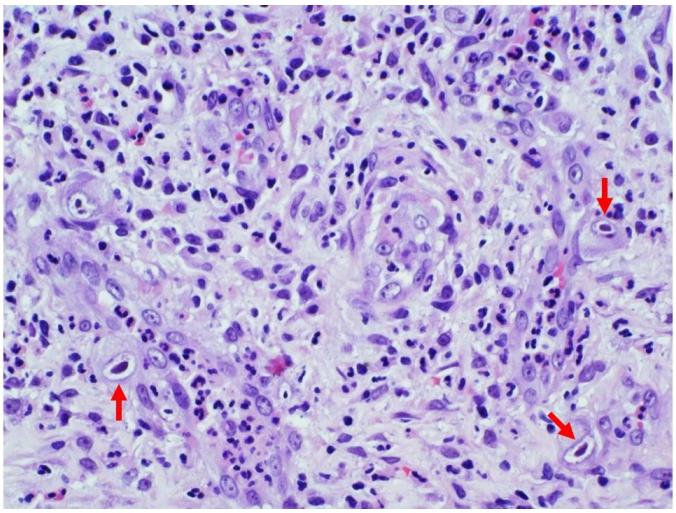

Figure 6. *Several cells (red arrows) show the characteristic CMV viral cytopathic changes with large intranuclear basophilic inclusions surrounded by a clear halo (so-called "Owl's eye" appearance) on magnification. H&E, 40×.*

Table 1. *The various therapy regimens employed for treatment of cutaneous CMV [4-56]. One patient's therapy was not detailed, thus the patient total is 57 rather than 58.*

The Medication Regimens Employed for Treatment of Cutaneous CMV			
Method of Treatment	**Concurrent Disease**	**Duration of Treatment**	**Number of Patients**
Ganciclovir	N/A	Ranges from days to months. 1 with indefinite therapy.	23
Ganciclovir + IVIg	Stevens-Johnson Syndrome	3 weeks	1
Ganciclovir + Foscarnet	CMV retinitis	N/A	1
Ganciclovir + Valacyclovir	N/A	3 weeks of ganciclovir followed by 2 months of valacyclovir	1
Ganciclovir followed by valganciclovir	N/A	Ranges from 2 weeks to 1 month	2
Valganciclovir	N/A	Indefinite	1
Valganciclovir	N/A	Ranges from 3 weeks to 8 months	13
Valganciclovir + IVIg	Wegener's granulomatosis	N/A	1
Valganciclovir followed by reduction of immunsuppressants	Post-renal transplant	5 months prophylaxis with valganciclovir after transplant plus 2 weeks after diagnosis of CMV, no resolution until discontinuation of antiviral and immunosuppressant	1
Excision	N/A	N/A, no recurrence	1
Fomentations/analgesics	N/A	N/A	2
Supportive	Gianotti-Crosti syndrome	N/A	1
Prednisolone + IVIg	DIHS	43 days	1
Prednisolone + IVIg + Gancivlovir	DIHS	1 month	2
Ganciclovir + methylprednisone	N/A	ganciclovir 2 weeks and methylprednisone 2 months	1
Ganciclovir + methylprednisone + topical hydrocortisone	Erythema multiforme	1 week	1
Valacyclovir	N/A	10 days	1
Valganciclovir	Microangiopathy	3 weeks	1
Valganciclovir + CMV-hyperimmuneglobulin IVIg + Eltrombopag	ITP	11 weeks with stable platelet counts	1
Valganciclovir + IVIg + Romiplostim	ITP	1 month with stable platelet counts	1
Total number of patients			**57**

IVIg used in combination with ganciclovir and one excision of a lesion in an immunocompetent patient with localized CMV reactivation; both had no recurrence of lesions. There were 13 total patient deaths reported throughout the review, yet only two could solely be attributed to CMV complications. The majority of deaths were as a result of sepsis or systemic fungal infection in immunosuppressed patients. Three patients were not directly treated for CMV, yet after addressing the immuncompromised state CMV resolved. This included two immunocompetent patients with vulvar ulcers that were only treated for symptomatic relief using either anti-inflammatories or wound dressings. One patient had recurring lesions over 3 years whereas the other had resolution with only small perforations remaining. The other patient that did not receive treatment was a pediatric patient diagnosed with

CMV induced Gianotti-Crosti syndrome (GCS), in which the skin lesions resolved within one month, as GCS is self-limiting [12].

There were several documented cases within our review of secondary ITP related to CMV. The normal treatment for ITP is corticosteroids and IVIg, but when the condition is secondary to another agent, the primary infection must be treated first before the typical therapies can be effective [13]. Most physicians will avoid corticosteroid treatment if CMV induced thrombocytopenia is correctly diagnosed because immunosuppression may have been the instigating factor for the CMV reactivation or infection [13]. This was demonstrated in two cases reviewed, as their initial suspicion was primary ITP and corticosteroids and IVIg were given [8, 13]. After the condition of the patients did not improve and viral testing was performed, the corticosteroids were tapered and valganciclovir started. One patient started romiplostim (a bone marrow stimulant) simultaneously with resolution of the viremia as well as improvement in the platelet count. The other patient was prescribed eltrombopag (a bone marrow stimulant) months later owing to unstable platelet counts. This patient was also unique because CMV hyperimmunoglobulin was employed along with the valganciclovir to combat the viremia. The remaining case with thrombocytopenia induced by CMV was diagnosed correctly immediately and treated successfully with oral valganciclovir.

The treatment protocol for DIHS patients with CMV is generally to administer corticosteroids, yet in the setting of atypical DIHS there is CMV reactivation that requires direct attention [14]. All the three patients within the review with this diagnosis were initially treated solely for DIHS. This included discontinuation of the offending medication. Subsequently, two patients were treated with prednisolone and another was given only supportive treatment to avoid immunosuppression. The patient that was never started on prednisolone was diagnosed with CMV after progression of symptoms and successfully treated with ganciclovir. IVIg was given to all patients, with significant relief of fever symptoms as well as skin eruptions. In fact, one patient's symptoms were resolved with a prednisolone restart along with IVIg after a trial of valacyclovir did not produce the desired effects. Another patient was not diagnosed with CMV until day 50, at which point IV ganciclovir was administered. This patient had significant resolution of cutaneous ulcerations, but shortly after developed severe CMV gastroenteritis and died of respiratory failure [14]. It was noted in the patients treated with prednisolone that cutaneous ulcers resulted after the corticosteroid taper was started and an argument could be made for immunosuppression as the reason behind CMV reactivation. However, one patient was not placed on the corticosteroids and still progressed with CMV and another patient was only on prednisolone for two weeks. It has been proven that short-term treatment of prednisolone does not cause unfavorable outcomes even in patients already immunocompromised with an HIV diagnosis [14]. This also supports the hypothesis that DIHS can cause reactivation of latent viruses [7]. The

Table 2. *The concurrent illnesses or diseases in patients diagnosed with cutaneous CMV.*

Associated Diseases in Patients with Cutaneous CMV	
HSV	10 [4, 6, 24-26, 30, 36, 39]
HIV/AIDS	8 [9,10,24,26,31,46,48,49]
Drug-induced hypersensitivity syndrome	3 [7, 14]
Immune thrombocytopenic purpura	2 [8, 13]
Antiphospholipid associated microangiopathy	1 [9]
EBV	1 [36]
Toxic epidermal necrolysis	1 [32]
Steven Johnson syndrome	1 [20]
Gianotti-Crosti syndrome	1 [12]
Leukocyte adhesion deficiency type 1 and Natural Killer cell deficiency	1 [45]
Common variable immune deficiency	1 [18]
Erythema multiforme	1 [55]

Abbreviations:
CMV- cytomegalovirus
DIHS- drug induced hypersensitivity syndrome
ITP- immune thrombocytopenic purpura
HSV- herpes simplex virus
IHC- immunohistochemistry
GCS- Gianotti-Crosti syndrome
PCR: Polymerase chain reaction

various treatments used for CMV throughout the literature are found in **Table 1**. The concurrent diseases in patients diagnosed with cutaneous CMV in addition to illnesses associated with immunosuppressive therapy leading to CMV are detailed in **Table 2**.

Conclusion

When thinking of CMV, associated symptoms such as gastroenteritis, retinitis, and pneumonitis may come to mind and are easily found in the medical literature. This is not the case when it comes to the cutaneous manifestations, yet these lesions may be more common than the literature leads one to believe owing to misdiagnosis. By far the most common form of skin lesion associated with CMV is ulcer, yet purpura, rashes, and erythema have also been documented among others. Diagnosis is largely done through skin biopsy and recognition of classic dense inclusions bodies, as well as through PCR, IHC, and blood antigen testing. Treatment with valganciclovir and ganciclovir has beneficial results, but the virus must first be correctly diagnosed, which can be difficult when cutaneous CMV does not have consistent characteristics or is hidden under coexisting conditions.

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