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Cytomegalovirus-Infected Cells in Granulation Tissue After Transurethral Resection of a Bladder Tumor: A Case Report

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Abstract

Cytomegalovirus (CMV) infection of the urinary bladder is primarily reported in immunocompromised patients. We describe a case of a 71-year-old male without a history of immunosuppressive therapy in whom CMV-infected cells were identified in the granulation tissue from a resection site 1.5 months after transurethral resection of a bladder tumor (TURBT). The initial TURBT specimen showed high-grade invasive urothelial carcinoma (pT1; muscularis propria invasion could not be excluded). On repeat TURBT, the resection site consisted of granulation and fibrotic scar tissue without residual carcinoma. Enlarged cells with intranuclear inclusions, predominantly in vascular endothelial cells, were positive for CMV on immunohistochemistry. Re-examination of the initial specimen did not reveal CMV-infected cells. The patient was asymptomatic, the lesion healed without antiviral therapy, and no recurrence of bladder cancer was observed during 1.5 years of follow-up. These findings support the interpretation that CMV infection was detected in the healing resection bed rather than being present at the tumor site before the initial resection. However, because CMV serology and blood and urine CMV testing were not performed, the timing and route of infection remained unclear. Possible explanations include systemic reactivation with hematogenous dissemination or reactivation in monocytes recruited to the wound; however, neither mechanism was established in this case. CMV should be considered in the differential diagnosis of unusual cytopathic cells in post-TURBT granulation tissue.

Categories: Urology, Pathology, Infectious Disease
Keywords: cmv infection, cytomegalovirus, granulation tissue, immunohistochemistry, transurethral resection of bladder tumor, urinary bladder, urothelial carcinoma

Introduction

Cytomegalovirus (CMV) is a ubiquitous herpesvirus that establishes lifelong latency following primary infection. Reactivation can result in tissue-invasive disease, particularly when cellular immunity is compromised [1]. CMV can infect multiple cell types, including epithelial cells, fibroblasts, and vascular endothelial cells [1,2]. Urinary bladder involvement, including hemorrhagic or ulcerative cystitis, has been primarily reported in patients with immunodeficiency, although cases in patients without recognized immunosuppression have been described [3-6]. Symptomatic CMV cystitis, which presents with hematuria or lower urinary tract symptoms and shows hemorrhagic or ulcerative mucosal lesions [3-6], should be distinguished from the incidental detection of CMV-infected cells in tissue from an asymptomatic patient. To the best of our knowledge, CMV-infected cells identified in the granulation tissue at the transurethral resection of a bladder tumor (TURBT) resection site have not been previously described.

Here, we report a case in which CMV-infected cells were identified in the granulation tissue during repeat TURBT. The absence of detectable CMV-infected cells in the initial specimen supports, but does not prove, secondary involvement of the healing resection site. We discussed the possible routes of infection while acknowledging that the available data do not establish when or how CMV infection occurred.

Case Presentation

A 71-year-old male was referred to our hospital after a health-check urinalysis revealed occult blood (2+). Voided urine cytology results were negative (class II). Ultrasonography revealed a left-sided bladder tumor (Figure *1A*), and cystoscopy revealed a 20-mm papillary tumor on the left lateral wall, near the expected location of the left ureteral orifice (Figure *1B*). Contrast-enhanced computed tomography revealed no metastasis.

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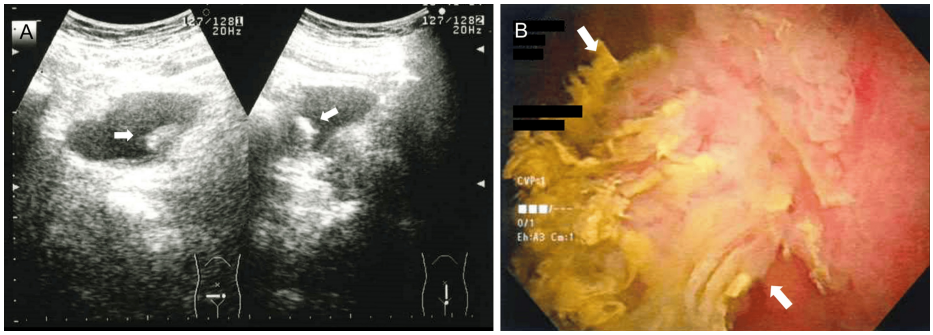


FIGURE 1: Ultrasonography and cystoscopy images of a left-sided bladder tumor.

(A) Ultrasonography showing a papillary mass (arrows) arising from the left wall of the urinary bladder; the left panel shows a transverse view and the right panel shows a sagittal view. (B) Cystoscopy showing a papillary tumor (arrows) on the left wall of the bladder. The left ureteral orifice is not visible in this image.

TURBT was performed for suspected bladder cancer. Although the left ureteral orifice could not be preoperatively identified, it was preserved during surgery. Pirarubicin was instilled intravesically immediately after surgery and retained for one hour. Histopathological examination revealed high-grade invasive urothelial carcinoma, staged as pT1; invasion of the muscularis propria could not be excluded. Lymphovascular invasion or concomitant carcinoma in situ was not identified.

Repeat TURBT was performed 1.5 months later. Cystoscopy revealed a resection scar lateral to the left ureteral orifice, with no other abnormalities; the scar was resected. Histopathological examination revealed granulation and fibrotic scar tissue without residual carcinoma. The granulation tissue contained enlarged cells with intranuclear inclusions, predominantly in vascular endothelial and stromal cells near small vessels (Figure *2*). Immunohistochemical analysis using anti-CMV monoclonal antibodies (clones CCH2 and DDG9; Agilent Dako, Santa Clara, CA, USA) revealed nuclear staining of these cells, confirming the CMV infection (Figure *2*, inset). To assess whether CMV infection was already detectable before the first resection, we re-examined the initial TURBT specimen, including deep resected tissue. No viral inclusions were observed on hematoxylin and eosin staining, and no CMV-immunoreactive cells were identified in the tumor or surrounding tissue.

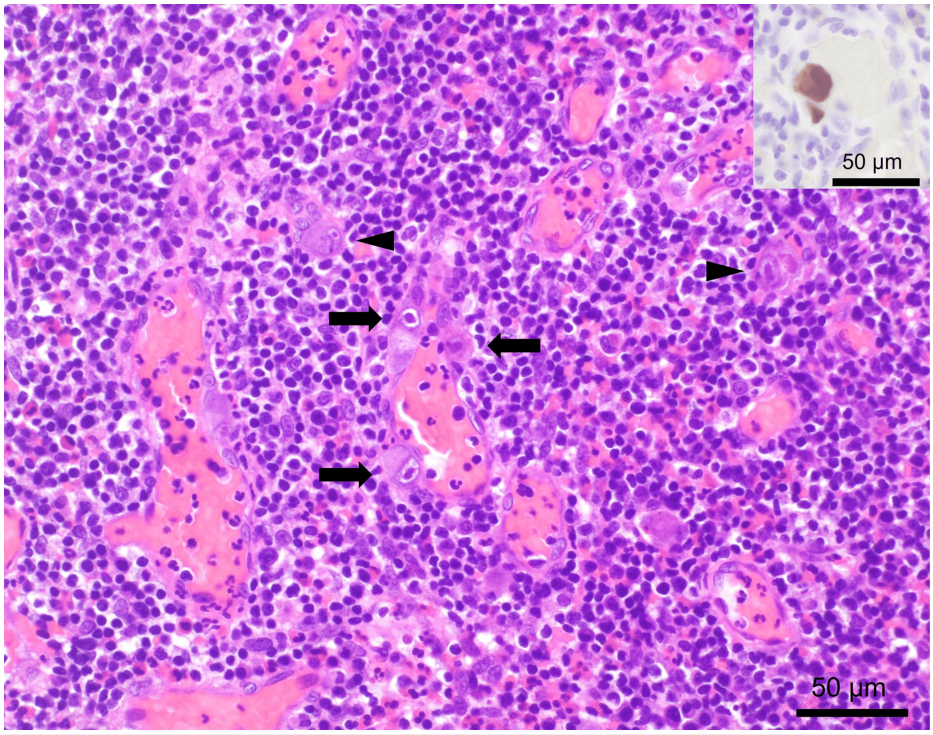


FIGURE 2: Cytomegalovirus-infected cells in the granulation tissue at the site of the second transurethral resection of a bladder tumor (TURBT).

Hematoxylin and eosin staining shows enlarged cells with intranuclear inclusions, predominantly endothelial cells of the capillaries (arrows) and stromal cells near the capillaries (arrowheads) in the granulation tissue. Inset: Cytomegalovirus (CMV) immunohistochemistry (clones CCH2 and DDG9) showing nuclear staining. Original magnification, ×400 (main image and inset). Scale bars: 50 µm.

The patient had no history of immunosuppressive therapy and was asymptomatic. Preoperative laboratory findings are summarized in Table *1*. Apart from a mildly elevated white blood cell count, no notable abnormalities were observed. Human immunodeficiency virus (HIV) testing was not performed.

Parameters	Patient values	Reference range
White blood cell count	8,450/μL	3,500–8,000/μL
Neutrophils	5,030/μL	1,250–5,850/μL
Lymphocytes	2,570/μL	900–4,000/μL
Monocytes	530/μL	70–700/μL
Eosinophils	260/μL	0–600/μL
Basophils	60/μL	0–100/μL
Red blood cell count	5.12 × 10^6/μL	4.10–5.50 × 10^6/μL
Hemoglobin	16.5 g/dL	13.4–17.4 g/dL
Platelet count	236 × 10^3/μL	123–331 × 10^3/μL
Fasting blood glucose	104 mg/dL	65–109 mg/dL
Hemoglobin A1c	5.3%	4.6–6.2%
Hepatitis B surface antigen	Negative	Negative
Hepatitis C virus antibody	Negative	Negative
Rapid plasma reagin test	Negative	Negative

TABLE 1: Preoperative laboratory findings.

After repeat TURBT, the patient underwent surveillance with urinalysis, urine cytology, and cystoscopy every three months. Intravesical Bacillus Calmette-Guérin therapy was reserved for recurrence according to the documented management plan. As the patient was asymptomatic and had no known immunosuppression, the CMV findings were managed expectantly without antiviral therapy, and blood and urine CMV tests were not performed. During follow-up, the patient showed no symptoms suggestive of systemic or organ-invasive CMV disease, including fever, malaise, abdominal pain, bloody stool, or visual disturbances. Urinalysis revealed no occult blood, and cystoscopy revealed a scarred resection site covered by normal-appearing mucosa. No recurrence of bladder cancer was observed during the 1.5 years of follow-up.

Discussion

CMV infection of the urinary bladder is rare and has often been described as hemorrhagic or ulcerative cystitis, particularly in immunocompromised patients [3-6]. In this patient, CMV-infected cells were found in the granulation tissue at the post-TURBT resection site, despite no known immunosuppressive therapy. The principal interpretive questions were whether CMV infection was already present at the tumor site before the initial TURBT and how the virus reached the healing resection site.

The initial TURBT specimen, including the sampled deep tissue, contained no viral inclusions or CMV-immunoreactive cells, whereas CMV-infected cells were identified in the granulation tissue at repeat TURBT and confirmed by immunohistochemistry. This sequence favors CMV involvement in the post-resection granulation tissue rather than infection that was already present at the tumor site before the initial TURBT. CMV has also been described in mucocutaneous ulcers, where its role may be secondary rather than causative [7]. However, the negative initial specimen does not establish that CMV was absent before surgery, because it represented only part of the bladder wall and immunohistochemistry for viral proteins cannot detect latent infection. Thus, the established finding is limited to active CMV infection in the healing resection bed; the onset and route of infection remain unclear, and the mechanisms discussed below are hypotheses that could not be tested with the available data.

The first hypothesis is systemic CMV reactivation around the time of surgery, followed by hematogenous dissemination to the wound. After primary infection, CMV persists in the CD34-positive hematopoietic progenitor cells and CD14-positive monocytes [1,8,9]. Immune-cell stimulation and inflammatory mediators, including tumor necrosis factor-α and catecholamine-associated stress signaling, have been associated with CMV reactivation in experimental or clinical settings [10-12]. CMV DNAemia has been reported in patients with critical illness not treated with immunosuppression [13]. These observations make systemic reactivation biologically plausible; however, they do not show that TURBT triggered reactivation in this patient. No perioperative blood CMV testing was performed, and the degree to which findings from patients with critical illness apply to routine TURBT remains unclear.

A second, potentially complementary hypothesis is the reactivation of latently infected monocytes recruited to the wound. An experimental study has shown that the differentiation of latently infected CD14-positive monocytes into macrophages or dendritic cells can be associated with reactivation, and interleukin-6 has been implicated in experimental models [14]. In an experimental study, differentiated macrophages supported greater CMV entry and productive infection than monocytes [15]. During wound healing, circulating monocytes enter the granulation tissue and differentiate in an inflammatory environment. Therefore, local reactivation, followed by spread to neighboring endothelial or stromal cells, is a plausible hypothesis. The predominance of infected endothelial cells in this case is consistent with this mechanism but does not prove it.

However, other routes cannot be excluded. CMV may be shed in urine [16]; therefore, the ulcer surface may have been exposed to the virus in the urinary stream. However, the predominance of infected endothelial cells within the granulation tissue does not specifically support an ascending or luminal route. Local reactivation of latent CMV in the bladder wall is another theoretical possibility, although a latent CMV infection of the bladder tissue has not yet been established. As the initial specimen did not include the entire bladder wall and tissue immunohistochemistry could not identify the latent virus, a small focus of pre-existing infection outside the sampled tissue cannot be ruled out.

The CMV finding appeared clinically self-limiting in this patient. Without antiviral therapy, the resection site healed with normal-appearing overlying mucosa, and no CMV-related symptoms were documented during 1.5 years of follow-up. This single observation does not establish that withholding antiviral therapy is appropriate. Management should be individualized according to symptoms, immune status, evidence of organ-invasive disease, and virological findings, when available. For pathologists, CMV-infected cells in post-TURBT granulation tissue may mimic atypical cells, making the correlation between morphology and CMV immunohistochemistry useful when the diagnosis is unclear.

This study had some limitations. CMV serostatus, blood and urine CMV DNA, and HIV status were not assessed, which limited the evaluation of the infection route and possible underlying immunodeficiencies. In addition, the initial specimen sampled only a part of the bladder wall, and the proposed mechanisms remain speculative; therefore, treatment or surveillance recommendations cannot be established.

Conclusions

CMV-infected cells were identified in the granulation tissue at the bladder resection site 1.5 months after TURBT in a patient with no known history of immunosuppressive therapy. The initial specimen contained no detectable CMV-infected cells, supporting the secondary detection of active infection in the healing resection bed; however, the timing and route of infection remain unclear. The lesion healed without antiviral therapy; however, this single case should not be used to establish a general treatment strategy. CMV should be considered when encountering unusual cytopathic cells in post-TURBT granulation tissue.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Kenji Yorita

Acquisition, analysis, or interpretation of data: Kenji Yorita, Daisuke Seto, Tadanori Hosokawa, Takushi Naroda

Drafting of the manuscript: Kenji Yorita, Daisuke Seto

Critical review of the manuscript for important intellectual content: Kenji Yorita, Daisuke Seto, Tadanori Hosokawa, Takushi Naroda

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Research Ethics Committee of Japanese Red Cross Kochi Hospital issued approval N/A. Formal ethics committee review was waived per institutional policy. This report was conducted in accordance with the Declaration of Helsinki. **AI use statement:** The authors used ChatGPT (OpenAI, San Francisco, CA) as follows: During preparation of this manuscript, the authors used ChatGPT (OpenAI, San Francisco, CA) to assist with gathering background information for the literature review. in Intruduction, Discussion. All information was verified against primary sources, and the manuscript was written and revised by the authors, who take full responsibility for its accuracy and integrity. The authors confirm that they have reviewed and verified all AI-assisted content and take full responsibility for the work. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following:

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