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Cytomegalovirus associated colonic pseudotumor: a consequence of iatrogenic immunosuppression in a patient with primary brain tumor receiving radiation and temozolomide

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Abstract

We report the case of a patient with primary brain tumor who developed cytomegalovirus associated colonic pseudotumor as an opportunistic infection while receiving chemotherapy with Temozolomide and radiation. This case highlights the potential for severe opportunistic infections in this patient population after severe immunosuppression.

Keywords

Cytomegalovirus; Pseudotumor; Temozolomide

Introduction

The standard treatment of high grade gliomas includes radiation therapy (60 Gy over 6 weeks) with daily temozolomide (75 mg/m^2 for 6 weeks) (TMZ) followed by 6 months of "adjuvant" TMZ (5 days/month at a dose of 150–200 mg/m^2) [1]. Glucocorticoids are added to control peritumoral brain edema if clinically indicated. Temozolomide (TMZ) is an orally available drug that is converted spontaneously to the active alkylation metabolite MTIC [(methyl-triazene-1-yl)-imidazole-4-carboxamide] and is approved for the treatment of anaplastic astrocytoma and glioblastoma multiforme (high grade glioma). An extended dose regimen of daily TMZ at 75 mg/m^2 provides continuous exposure of tumor cells to the drug and delivers substantially higher total drug compared to standard regimen (5 days/month at a dose of 150–200 mg/m^2). A study by Su et al. reported TMZ-induced lymphopenia in patients receiving extended dose regimens [2]. This resulted in few cases of opportunistic infections related to T cell dysfunction including Pneumocystis Carinnii pneumonia (PCP) which prompted to the use of prophylactic therapies for PCP in patients with extended dose regimen. There are still unknown clinical implications we continue to realize with the more widespread use of Temozolomide. We report the first case of cytomegalovirus-associated colonic pseudotumor in a patient with primary brain tumor presenting as an opportunistic infection while receiving extended dose regimen of TMZ, radiation and glucocorticoids for treatment of high grade glioma.

Case report

A 68-year-old female presented with cognitive changes, confusion and memory loss. A brain MRI demonstrated a 4.0 × 3.8 × 3.5 cm mass in the left temporal lobe with extension

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to left parietal lobe. She underwent surgical debulking of the lesion and pathology was consistent with a Gliosarcoma (grade IV astrocytoma). Six weeks post-operatively she began a course of standard radiation (60 Gy over 6 weeks) with concurrent daily TMZ (75 mg/m^2 for 6 weeks). During the fourth week of this therapy she suffered a left posterior internal capsule cerebrovascular accident and during the fifth week her platelet count fell to 30,000 and TMZ was discontinued. She remained on tapering doses of dexamethasone and continued trimethoprim-sulfamethoxazole for pneumocystis carinii pneumonia (PCP) prophylaxis while she continued with radiation therapy.

Towards the end of the fifth week of treatment, she developed 4 days history of diffuse abdominal pain, low grade fevers and three episodes of hematochezia prompting admission to the hospital. CT scan of abdomen and pelvis (Fig. 1) demonstrated a soft tissue hypodensity with lumen collapse suggestive of a mass like process at the rectosigmoid junction and early diverticulitis. Her symptoms persisted after 2 weeks of therapy with ciprofloxacin and metronidazole. Colonoscopy (Fig. 2) revealed a large sigmoid mass 28 cm from anal verge. The lesion appeared consistent with a primary or metastatic neoplasm and virtually obstructed the lumen making it impossible for the colonoscope to be advanced beyond the mass. Biopsy specimens (Fig. 3) from this lesion were diagnostic for cytomegalovirus (CMV) colitis with pseudomembrane formation, demonstrating CMV inclusions. Serum studies revealed CMV PCR greater than 50,000 copies, positive CMV IGG by ELISA, negative IGM, negative HIV by ELISA and total CD4 count of 36. Intravenous therapy with Ganciclovir (5 mg/kg every 12 h) was started with rapid improvement of her abdominal pain. However, 1 week later the patient developed peritoneal signs leading to exploratory surgery. Perforation of the bowel was noted resulting in a diverting colostomy and resection of the sigmoid colon. The surgical pathology revealed an area of gross perforation with active CMV colitis, mucosal ulceration, transmural inflammation and abscess formation. There was no evidence of neoplasm or malignancy. She continued therapy with ganciclovir without further abdominal pain, bleeding or fevers. Other opportunistic infections during this hospitalization included oral candidiasis and herpes labialis. Her persistent thrombocytopenia and other active problems precluded the planned administration of post-radiation adjuvant TMZ. The patient's right side hemiparesis that followed her CVA persisted and she and her family opted for comfort and supportive care measures only. She was transferred to a nursing facility and continued ganciclovir until she died a total of 4.5 months following the original surgery for her gliosarcoma.

Discussion

CMV infections are most common in the HIV population but are rare in solid tumor patients. Gastrointestinal involvement with CMV can result in gastroenteritis, duodenitis, ileitis, colitis, proctitis or exacerbation of inflammatory bowel disease. Rarely, this presents with polypoid masses on radiographic imaging that are referred to as pseudotumors. Only 14 cases of CMV pseudotumors presenting in the colon have been reported in the English literature [3–13]. These are reported in severely immunocompromised hosts with HIV-AIDS or organ transplants patients. None have previously been reported in patients with primary brain tumors. The clinical presentation typically includes abdominal pain, changes in bowel movements, diarrhea, hematochezia and fever. The management and outcome is variable with some patients responding to Ganciclovir and others been unresponsive to antiviral therapy and requiring surgical excision.

The patient described above was HIV negative but was severely immunosuppressed with total CD4 count of 36. An ongoing study has documented that patients with high grade gliomas begin therapy with normal CD4 counts which fall rapidly over the first 2 months as a result of the glucocorticoids, radiation, and temozolomide that they receive [14].

Glucocorticoids are known to be highly lympholytic and result in immunosuppression [15, 16]. Deaths from PCP pneumonia in brain tumor patients receiving glucocorticoids have prompted clinicians to routinely administer PCP prophylaxis. Radiation therapy to a localized region of the brain can contribute to additional myelosuppression probably as a result of radiation to circulating hematopoietic stem cells [17]. Modeling studies suggest that circulating lymphocytes will receive substantial radiation when exposed to a total of 30 min of radiation therapy administered over 6 weeks. TMZ is also a selective CD4 toxin; even though its toxicity was considered manageable in early phase trials, lymphopenia can occur with the use of extended dose regimens [18, 19]. This lymphopenia was also noted in patients with melanoma [2, 20] and neuroendocrine tumors [21] treated with TMZ even without concomitant radiation or glucocorticoids. TMZ-induced lymphopenia can be severe and prolonged for several months after discontinuation of therapy [2, 21] and appears to predispose to opportunistic infections (OI) in this subset of patients. During the past years, an association of CMV with malignant gliomas has been described [22]. Mitchell et al. found that 80% of patients with newly diagnosed glioblastoma multiforme (GBM) had detectable human cytomegalovirus in peripheral blood and control patients did not [23]. In view that GBM patients can have subclinical CMV-viremia at diagnosis, subsequent CMV-related opportunistic infections may become more prevalent as combined immunosuppressive therapies, including TMZ reduce CD4 counts below 50. Several OI reported to date include PCP [24, 25], Listeria Brain abscess [26], *Aspergillus* pneumonia [2], Kaposi Sarcoma [26], cryptococcal meningitis [27] and one case of disseminated CMV with associated colitis and transverse myelitis [21]. Su et al. also observed other infections indicative of T cell dysfunction including herpes simplex, herpes zoster and mucocutaneous candidiasis [2].

The current standard approach for treatment of high grade gliomas includes radiation therapy (60 Gy over 6 weeks) with daily temozolomide (75 mg/m^2 for 6 weeks) followed by 6 months of “adjuvant” TMZ (5 days/month at a dose of 150–200 mg/m^2) [1]. This therapy is administered in combination with PCP prophylaxis. Glucocorticoids are given to control peritumoral brain edema when indicated, but are not inevitably part of therapy. Although this approach has been clearly shown to improve survival, it does result in severe iatrogenic immunosuppression in a substantial number of patients. This case highlights the potential for severe opportunistic infections in this patient population and represents the first case of cytomegalovirus associated colonic pseudotumor in a patient with primary brain tumor presenting as an opportunistic infection after severe immunosuppression. Physicians should be aware of these risks and complications while providing treatment to these patients and consider obtaining routine CD4+ counts. Further studies are warranted to investigate the outcome of severely immunosuppressed brain tumor patients and potential added immunosuppression that may accompany more intense and prolonged temozolomide treatment schedules.

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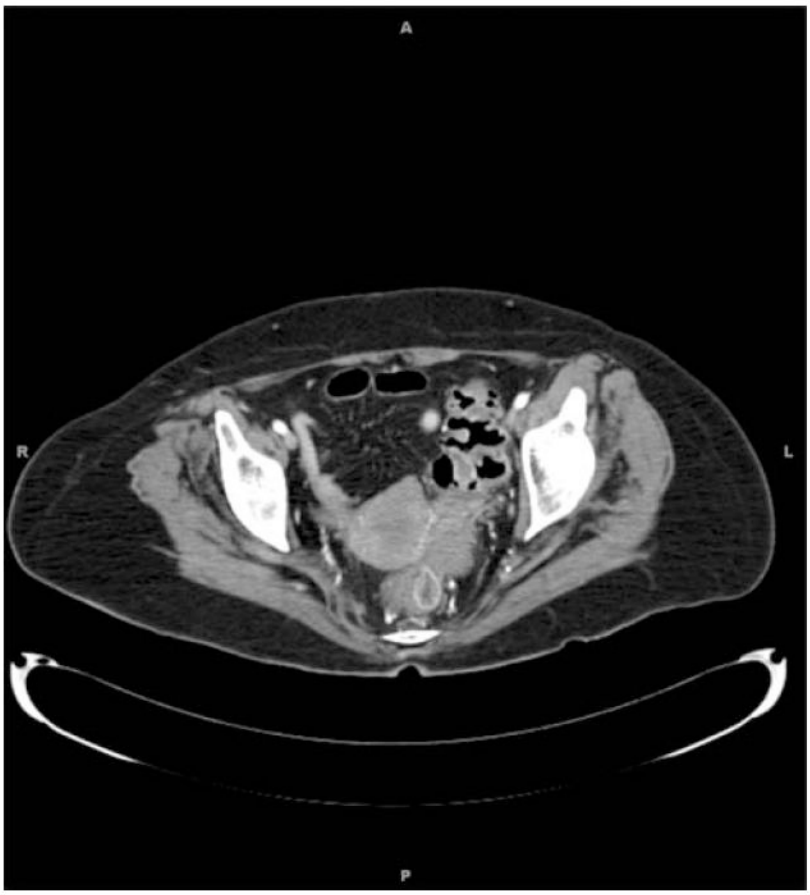

Fig. 1.
Soft tissue hypodensity with lumen collapse suggestive of a mass like process at the rectosigmoid junction

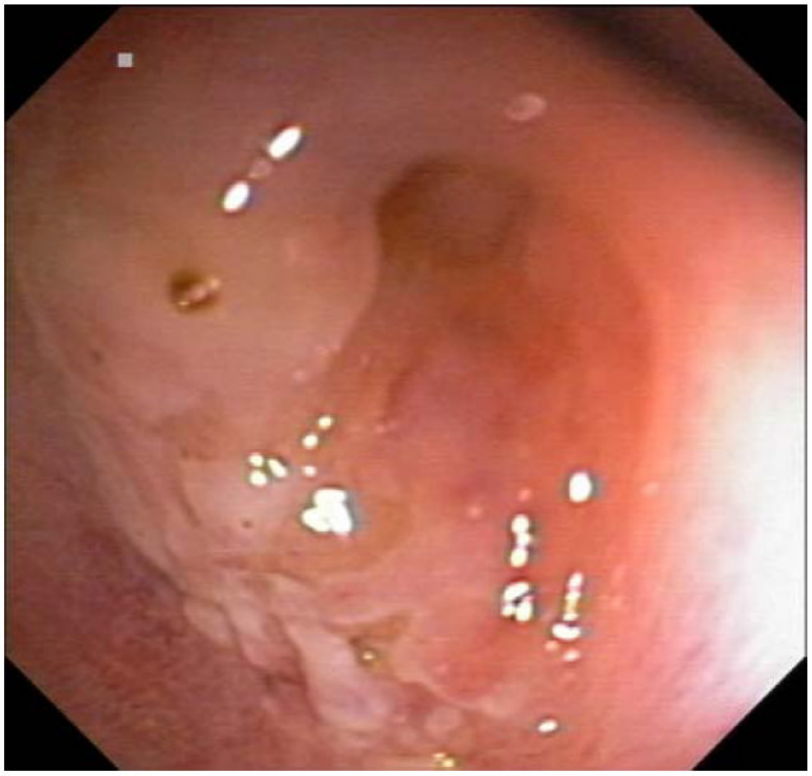

Fig. 2.
Colonoscopy revealed a sigmoid mass 28 cm from anal verge that obstructed the lumen. The colonoscope could not be advanced beyond the mass

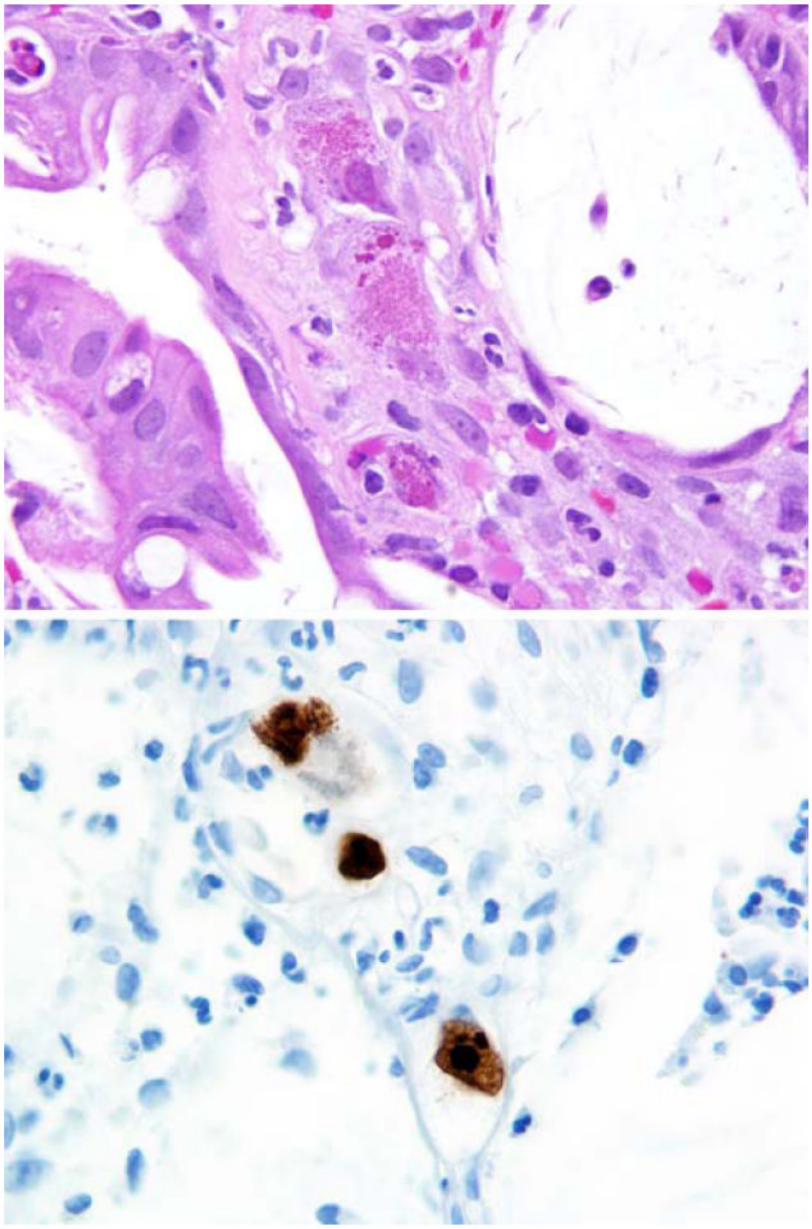

Fig. 3.
Biopsy specimens demonstrating cytomegalovirus inclusions bodies