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Pseudotumor presentation of CMV disease: diagnostic dilemma and association with immunomodulating therapy

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40 word summary: Atypical presentations of CMV, including pseudotumors, have been reported in the literature. We describe two cases in the setting of new immunomodulatory therapy and review the literature. It is possible that such cases will be increasingly encountered in the setting of new immunotherapies.

Abstract

Cytomegalovirus is a significant cause of morbidity and mortality in the immunocompromised host. Atypical presentations which include pseudo tumors or 'cancer mimics' have been described. The etiology of these lesions remains unclear. The authors describe two previously unpublished cases that have arisen in the context of newer immunomodulating therapy and review the existing non-HIV associated CMV pseudo tumors described in the literature.

Introduction

Cytomegalovirus (CMV) infection is a significant cause of morbidity in immunocompromised patients where a predictable spectrum of illness has been well described. Atypical presentations of CMV infection, including those mimicking mass lesions, otherwise known as pseudo-tumours, have been occasionally reported in the literature. These lesions were first seen in the

context of significant immunosuppression associated with human immunodeficiency virus (HIV) but more recently, cases have been described in the non-HIV setting. Here within, the authors present two cases in patients receiving newly developed immunomodulatory therapy in the form of pembrolizumab for the management of cancer and belatacept in a kidney transplant recipient. A review of other non-HIV cases reported in the literature was also undertaken to gain a better understanding of this unusual presentation.

Cases

Case 1:

A 59-year-old female presented with a three-week history of a progressively enlarging painless oral cavity mass (Figure 1). A mucosal squamous cell carcinoma (SCC) of the retro-molar trigone was diagnosed 11 years prior and the patient underwent a marginal mandibulectomy and subsequently, a modified radical neck dissection followed by post-operative chemoradiation with cisplatin and 60Gy of external beam radiation after developing nodal disease in the neck. She received a further 45Gy of radiation with concurrent cisplatin chemotherapy after developing further nodal disease 24 months after her initial treatment. After 6 years, she presented with extensive local recurrence, not amenable to curative treatment and was enrolled in a clinical trial to receive combination carboplatin and fluorouracil chemotherapy and the PD-1 check-point inhibitor, pembrolizumab. Eight months into this protocol, the patient developed a rapidly enlarging painless ulcerated mass at the prior operative site of disease. On ^{18}F-fluorodeoxyglucose positron-emission tomography (^{18}FDG-PET/CT) the lesion was highly avid and relapse of malignant disease was assumed (Figure 2). The mass was subjected to three biopsies, all of which demonstrated ulcerated granulation tissue with very focal viral cytopathic changes with immunohistochemistry staining positive for CMV (and for which immunostains for other Herpes virus were negative)and without evidence of malignancy. Testing for HIV with a fourth-generation assay and CMV viral load (VL) on peripheral blood were both negative. Lymphocyte subsets analysis showed a CD4 T-cell count of 350 x 10^6m/L (normal 450-1700 x 10^6m/L). The patient received ganciclovir 5mg/kg every twelve hours for 28 days with some appreciable clinical reduction in size of the lesion before transitioning to oral therapy with 900mg valganciclovir twice daily for a further 28 days. She also received a short course of oral prednisolone 25 mg daily for 5 days. At the completion of 8 weeks of antiviral therapy, there had been only a partial reduction in the size of the lesion and the patient proceeded to surgical

resection which demonstrated persistent CMV cytopathic change and immunostain positivity.. Now, 30 months post resection the patient remains well without evidence of recurrence.

Case 2:

A 52-year-old female presented 12 months after her second living unrelated kidney transplant with high risk CMV serostatus (CMV D+/R-) with 6 months of a slowly growing vulval lesion without systemic symptoms (Figure 3). The lesion was associated with intermittent bleeding and local tenderness. Her post-transplant course was complicated by early calcineurin inhibitor-associated nephrotoxicity and she was switched from tacrolimus to monthly infusions of belatacept 5mg/kg around day 90 post-transplant. Her other immunosuppression included prednisolone 5mg daily and mycophenolate mofetil 250mg twice daily. Onset of this lesion was preceded by 3 months of asymptomatic but persistent low level CMV viremia (ranging between 625 – 7563 IU/mL in plasma) without evidence of end organ disease. Viremia persisted despite administration of appropriately renally dosed valganciclovir and resistance was subsequently detected at M460V in the UL97 gene by gene analysis. Subsequent CMV management was based on reduction in immunosuppression and CMV immunoglobulin (a total of four doses administered). During this period of prolonged viremia, she developed the slowly enlarging vulval lesion, initially thought to represent simple warts. She proceeded to biopsy which demonstrated severe squamous dysplasia and the decision was made to resect the lesion due to concerns regarding potential malignancy. She underwent right-sided radical wide local excision of the right upper hemi-vulva and left vulvar wide local excision of the lower left hemi-vulva and posterior fourchette. Pathology demonstrated extensive severe squamous dysplasia, chronic inflammation and evidence of cytomegalovirus infection with cytopathic effect. Immunostain for CMV was strongly positive (and for which immunostains for other Herpes virus were negative). The inflammatory infiltrate was found to contain predominantly CD3+ T-cells, CD20+ B-cells and numerous plasma cells that were polytypic by *in situ* hybridization for kappa and lamda immunoglobulin light chains, not consistent with a post-transplant lymphoproliferative disorder. Testing for HIV with a fourth-generation assay was negative and lymphocyte subsets demonstrated a CD4 count of 58 cells/uL (normal range 348 – 1456 cells/uL). Soon after resection, she transitioned from belatacept back to tacrolimus and now 20 months post resection she remains well, without evidence of recurrence.

Materials and Methods

Additional cases of CMV pseudotumors were identified from the literature using a PubMed search (1980 – October 2019) of the English language medical literature applying the terms 'CMV', 'pseudotumor' and 'Inflammatory mass'. Cases associated with HIV infection were excluded. References in identified articles were examined for additional reports. A case met inclusion criteria if a lesion resembling a tumor was described macroscopically or radiologically in combination with features consistent with CMV infection on histopathology. CMV-associated tissue involvement was defined by the presence of cytopathic effects with intranuclear inclusions +/- positivity for CMV immunohistochemistry. The inflammatory infiltrate within tumors was defined as either intense inflammation or unquantified due to heterogeneity in description between reports. The outcome of the lesion was defined as either clinically or endoscopically resolved, showing signs of healing or unknown.

Based on the small number of cases identified, simple descriptive statics were utilized. Continuous variables were expressed as a median (range) and categorical variables as frequency (percentage).

Analysis of biopsy tissue from Case 1 Sample digestion and flow cytometry analysis

A biopsy of the oropharyngeal mass from the Case 1 was minced with a scalpel followed by digestion with Collagenase III (3mg/mL) (Worthington) and DNase I (3mg/mL) (Roche) in RPMI (Thermo) with 2% FBS (Sigma) for 30 minutes at 37°C with agitation. Digested tissue was strained (40 M) and washed in PBS with 2% FBS. For flow cytometry, single-cell suspensions were stained with panels of antibodies recognizing: human CD4 (RPA-T4; APC-H7), CD8 (RPA-T8; APC), CD3 (SK7; PE-Cy7), CD19 (HIB19; SK7), CD14 (M5E2; BV421), CD16 (3G8; BV650), CD56 (NCAM16.2; BV605), PD-1 (EH12.1; BV650), HLA-DR (G46-6; PerCP) (All BD Biosciences). Dead cells were excluded using propidium iodide. Cells were analyzed on an LSR Fortessa (BD Biosciences) and data was analyzed using FlowJo software (LLC).

Histology and immunohistochemistry

A biopsy of the oropharyngeal mass was fixed in 10% buffered formalin and paraffin-embedded. Sections were stained with haematoxylin / eosin, or using for immunohistochemistry (IHC). For PD-L1, CD3, Myeloperoxidase (MPO), Vimentin IHC, sections underwent antigen retrieval

using citrate buffer (DAKO) followed by staining with either rabbit anti-human PD-L1 (clone: 28-8) (Abcam), or anti-CD3 (DAKO), anti-MPO (DAKO), anti-vimentin (Cell Signaling Technology) (all rabbit polyclonal). All were probed with anti-rabbit HRP-conjugated secondary antibody (DAKO). Stains were developed using DAB substrate (DAKO), following by haematoxylin counterstaining.

Results

Review of the literature yielded an additional 21 cases of non-HIV associated CMV pseudotumor in addition to the two cases described in this report (Table 1). Patient age at the time of diagnosis ranged from 40-89 years with a median of 62 years and 61% (14/23) were male (Table 1). Pseudotumors were located in the gastrointestinal tract in 78% (18/23) of instances (colon N=11, rectum N =4 and stomach/small bowel N = 3), lung (N =2), the head and neck region (N=2) and vulva (N=1). Eleven (48%) of patients were known to be immunosuppressed, including 7 recipients of solid organ transplant (kidney transplant N=5, heart transplant N=2). Thirteen patients (57%) underwent HIV testing, all which were negative, and 6 patients underwent T cell subset analysis with CD4 counts ranging from 36-706 cells/uL. Peripheral CMV testing was undertaken in 8 patients, 4 of whom were found to have concurrent CMV viremia.

Clinical manifestations

Ninety six percent (22/23) of patients presented with focal symptoms relating to the site of the lesion, that had lasted a median of 15 days (range 1-224 days) prior to seeking care. All but one of the 18 patients with gastrointestinal pseudotumor presented with gastrointestinal symptoms including abdominal pain (N=13), diarrhea (N=6), fevers (N=5), constipation (N=3). Patients with extra-intestinal pseudotumors did not present with gastrointestinal symptoms.

Radiological features

Nine patients underwent radiologic studies to evaluate symptomatology. This included 5 of the cases with gastrointestinal pseudotumors that underwent abdominal computed tomography (CT), 3 of which identified focal pathology concerning for a malignant lesion and 2 of which found no lesion visualized. Both patients with pulmonary pseudotumors presented with lung masses, one of which was cavitary and associated with hilar lymphadenopathy. The first case presented in this report is the first published report demonstrating the ^{18}FDG-PET/CT characteristics of these lesions, which showed an avid mass, concerning for malignancy (Figure 1).

Diagnosis methods

All pseudotumors were diagnosed based on microscopic findings on anatomical pathology specimens. CMV cytopathic effects characterized by intranuclear inclusions were identified in 100% of cases (23/23). CMV histochemistry was undertaken in 19 cases and was positive in all. One case was also CMV culture positive. Based on non-standardized reporting between cases, dense or intense inflammatory infiltrate was described in 7 cases while the remaining were not quantified.

Management

Surgical management was undertaken in 7 instances; wedge resection of pulmonary lesions (N=1), wide local incision of vulval lesion (N=1) and bowel resection (N=5), with one of these cases undertaken emergently in the setting of a colonic perforation. Thirteen patients were treated with antiviral therapy; ganciclovir (N=12) followed by valganciclovir (N=3) and valganciclovir only (N=1). Two patients received CMV immunoglobulin. Patients were treated with antivirals for a median of 26 days (range 14-126 days). Four patients were lost to follow up but of the remaining, follow-up was reported for a median of 22 weeks (range 2-208 weeks). At follow up, 21 cases demonstrated either endoscopic or clinical resolution of lesions, while two case, include case 1 in this report, had persistent pseudotumor albeit with signs of healing.

Tissue analysis from case 1

Immunohistochemistry analysis of biopsies from case 1 revealed intense myeloperoxidase staining indicating extensive neutrophil infiltration and de-granulation into pseudotumor as stained by vimentin to distinguish from healthy tissue. Extensive CD3 staining was also present throughout the pseudotumor, colocalizing with PD-L1 staining on non-immune cells. This immune infiltrate profile was recapitulated in flow cytometry analysis of fresh resected tissue, which also revealed moderate infiltration of monocyte populations.

Discussion

CMV associated pseudotumors were first reported in patients with profound immunosuppression in the era of HIV-AIDS. More recently, pseudotumors in the non-HIV setting have been described in the literature in both the immunocompetent and in non-HIV immunocompromised host. Here, we described the first two cases of non-HIV-associated pseudotumor in the setting of immune check point inhibitor therapy and soluble fusion protein therapy and review the existing cases of non-HIV associated CMV pseudotumor reported in literature.

CMV is a ubiquitous virus, typically acquired early in life, that infects and then establishes latency in the host in a wide variety of cells including epithelial cells of glandular and mucosal tissue, smooth muscle cells, fibroblasts, macrophages, dendritic cells and vascular endothelial cells (1, 2). Under certain circumstances, particularly in the setting of immunosuppression, CMV can reactivate and cause tissue invasive disease. Target organs for CMV include the lung, retina, gastrointestinal tract and the liver. While CMV tissue invasion is well described, the pathogenesis of CMV pseudotumor formation is not. CMV DNA products are known to be involved in cell cycle dysfunction, genomic instability, cell immortalization, down regulation of the host immune response and anti-apoptosis but evidence for a causative role in either pseudo-oncogenesis or oncogenesis is currently lacking (3, 4). Reports of CMV antigens and DNA detectable in several human cancers (including glioblastoma) have been conflicting and there is currently no definitive evidence to support a role for CMV in the pathogenesis of human cancers (3-8). Whether CMV associated pseudotumor growth represents superinfection in areas of existing inflammation or a localized, primary inflammatory response to the virus itself, in the setting of continuous shedding from mucosal surfaces, is unknown (9).

The first description of a CMV associated pseudotumor was an infant with a pyloric obstruction, closely followed by an adult case with gastric antrum obstruction, both in the setting of advanced HIV infection (10, 11). Both cases were found to have an exophytic mass on endoscopy with histology demonstrating CMV inclusions with an absence of additional or alternative pathology. Examples of multifocal CMV-associated gastrointestinal pseudotumors in Macaques infected with simian immunodeficiency virus soon followed these reports (12). In the historical setting, CMV pseudotumors have been almost exclusively associated with advanced HIV however, appreciation that these lesions can affect a spectrum of patients, including those otherwise not considered to be immunosuppressed, is growing. While there is no universally accepted marker for net state of immunosuppression it is interesting to note that a breadth of CD4 T-cell counts were reported in the non-HIV pseudotumor cases reviewed.

In the setting of HIV, CMV pseudotumors have almost entirely been described in the gastrointestinal tract (9, 13). While a similar trend was observed in the non-HIV cases reviewed, the 25% of cases identified outside the gastrointestinal tract serve as an important reminder not to discount this pathology in non-GIT associated lesions. Patients often presented with symptoms related to the affected organ due to mass effect and both radiological and macroscopic features

247 are suggestive of malignancy. Diagnosis is one of exclusion and based entirely on histological
248 features in excised tissue. Histopathological findings typically consist of CMV cytopathy with
249 positive immunohistochemistry without an alternative pathology. Optimal management of CMV-
250 associated pseudotumors is unknown, and whether there is any role for antivirals as part of the
251 pseudotumor strategy in attaining cure remains unresolved. An attempt at antiviral therapy was
252 considered worthwhile for case 1 due to the considerable mortality associated with a resection
253 but evidence from the literature would suggest that the majority of cases either spontaneously
254 resolve or respond to excision, particularly when in the gastrointestinal tract.
255 The establishment of the pseudotumor at the precise site of prior SCC treatment, as described in
256 Case 1, is peculiar and the authors can only speculate whether there is a unique pathogenesis to a
257 CMV pseudotumor formation in this context. CMV has been shown to reactivate in blood
258 monocytes and macrophages and shed from mucosal surfaces, particularly from the oral mucosa,
259 both in times of wellness and stress. Functional impairment of antigen specific T cells (or T cell
260 'exhaustion') is a defining characteristic of many malignancies and chronic viral infections(14,
261 15). This 'exhaustion' phenotype appears to be mediated by a number of immune checkpoints.
262 The use of immune checkpoint inhibitors such as pembrolizumab, a PD-1 antibody, to release the
263 immunological brakes on host anti-tumor immunity, has been a significant advance in cancer
264 therapy(16). It is possible that the patient may have had increased CMV shedding at the prior
265 resection site in the setting of localized trauma and then, with the addition of an immune
266 checkpoint inhibitor, experienced restoration of viral specific T-cells in the oral associated
267 mucosa leading to an exaggerated inflammatory response, akin to a localized immune
268 reconstitution inflammatory syndrome (IRIS) to tissue associated CMV antigens. In agreement
269 with this hypothesis, IHC revealed localized PD-L1 expression within the pseudotumor in the
270 vicinity of infiltrating T cells. This was coincident with extensive neutrophilic infiltration and de-
271 granulation. While CMV staining was only rarely detectable, even a small reactivation event in
272 the context of immune checkpoint blockade may be sufficient to trigger such a cascade. Using
273 immune checkpoint inhibitor therapy to restore viral specific T cell responses, in the setting of
274 chronic infection is under investigation as a novel approach to HIV and hepatitis B (17, 18). On
275 review of pseudotumor tissue prior to antiviral therapy, we identified PD-1+ T cells infiltrating
276 the environment surrounding cells with cytopathic effect and reactivated virus. While the
277 pseudotumor was comprised primarily of granulocytic infiltrates and fibrotic tissue, there were

extensive areas of PD-L1+ staining, suggesting that, upon cessation of pembrolizumab, local T cell-driven inflammation might largely be contained. This theory is purely speculative, especially given that we might have expected a better clinical response to high dose steroids had this lesion represented a primarily inflammatory response.

Belatacept based immunosuppression, as compared with tacrolimus based immunosuppression, is increasingly utilized for renal transplant recipients due to its association with improved long-term patient and graft survival (19). However, belatacept is associated with a paradoxical increased risk of infection, particularly EBV and CMV, but whether this is due to potent a T-cell activation inhibition or impaired viral immunity is unclear (19). There has been an observable risk of post-transplant lymphoproliferative disorder (PTLD) in patients receiving belatacept who are EBV seronegative, suggesting that the primary acquisition of the virus after transplant, in the absence of immunity, leads to uncontrolled EBV replication and progression to PTLD (20, 21). This observed risk has resulted in a black box warning against the use in this setting. Calcineurin inhibitors affect both naïve and memory T cells while belatacept directly targets the pathway required largely for naïve responses seeming to relatively spare T cells that have prior antigen experience (22). This would suggest that in the setting of viral naivete, there may be a distinct vulnerability to immune incompetence (22)**.** Whether we will see more atypical viral infection, including CMV, with increasing use of belatacept will be borne out in post marketing literature and case reports.

The two cases of pseudotumor formation described here within are important because they demonstrate that while the histological consequence of a pseudotumors mass is consistent between cases, the immunological context in which they develop is not. The authors speculate that pseudotumor formation in case 1 is most likely secondary to an enhanced or restored immunological response in the setting of check point inhibition while the case 2 is most likely due to an impaired naïve T cell immune response in the setting of co-stimulation blockade. Interestingly both lesions are associated with a similar observed histological inflammatory response in tissue. These cases highlight serve to highlight the limits to our understanding of the immunological circumstances under which these lesions develop.

Conclusion

CMV tumors are an uncommon occurrence but despite the traditionally held assumption that they affect HIV patients only, there is increasing evidence that non-HIV patients may also be

affected. A high index of suspicion is required as they closely mimic malignancy and early attempts to obtain tissue for histological management are necessary to attain the diagnosis. Because the immunologic and viral mechanisms that govern this phenomenon are unclear, and likely heterogenous, so too is the natural history and optimal management. The role for either antivirals or surgery is unknown, although based on this series, the prognosis of such lesions in the short to medium term would appear to be good, with treatment decisions made on a case-by-case basis. With the increasing adoption of immune modulating therapy to treat a variety of autoimmune, immunological and malignant conditions, it is possible these lesions may become more frequently observed in clinical practice.

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Figure 1. Fungating ulcerated lesion on oral mucosa of the left lower mandible at the site of prior SCC resection and marginal mandibulectomy

Figure 2. Sagittal images of a ^{18}F-fluorodeoxyglucose positron-emission tomography of the head and neck demonstrating an avid lesion on the left lower jaw at the site of ulcero-fungating mass

Figure 3. 6cm cluster of verrucous papules in a cluster encompassing the entire right labia minora, the right clitoral hood and the margin of the right labia majora and sparing the periurethral area

Table 1. Characteristics of CMV pseudotumors

Author (year)	Site of involvement, age, sex	Immunocompromised status	Clinical	Histology	Treatment	Outcome
Lionaki et al.**(23)**	Colon 64M	Kidney transplant 23 years prior (CMV +/+) (MMF + CyA)	Months of fatigue, headache, dizziness and 7% LOW	Intense inflammation, intranuclear inclusions, IHC +	Ganciclovir 21 days then valganciclovir for 63 days	Endoscopic healing
Kawasaki et al.**(24)**	Caecum 76M	NIL	4 days of lower abdominal pain	Inflammation NQ, intranuclear inclusions, IHC +	NIL	Endoscopically resolved
De Jesus et al.**(25)**	Rectosigmoid junction 68F	Gliosarcoma with radiotherapy and temozolomide + dexamethasone	Abdominal pain, fevers, hematochezia	Inflammation NQ, intranuclear inclusions, IHC ND	Ganciclovir for 126 days	Palliated
Jacob et al.**(26)**	Rectum 76F	NIL	1 week constipation, anal and abdominal pain, bloating	Intense inflammation, intranuclear inclusions, IHC +	Ganciclovir for 14 days	Endoscopically resolved
Shah et al. **(27)**	Rectum 42M	NIL	3 months of small volume bloody diarrhea with 13kg LOW	Intense inflammation, intranuclear inclusions, IHC +	Ganciclovir IV for 21 days	Endoscopically resolved
Patel et al. **(28)**	Rectosigmoid junction 89F	NIL	5 months constipation and tenesmus	Inflammation NQ, intranuclear inclusions, IHC +	NIL	Endoscopically resolved
Friedman et al.**(29)**	Larynx 62M	Neurofibromatosis	2 weeks of progressive SOB and stridor	Inflammation NQ, intranuclear inclusions, IHC +	NIL	Endoscopically resolved
Garcia et al. **(30)**	Stomach 44M	NIL	15 days fevers, malaise, mid-epigastric pain	Inflammation NQ, intranuclear inclusions, IHC ND	NIL	Endoscopically resolved
Crespo et al.**(31)**	Colon 62M	Heart transplant (CMV +/+) CyA + AZA	12 hours abdominal pain, constipation, hematochezia	Inflammation NQ, intranuclear inclusions, IHC +	Ganciclovir 28 days + CMV immune globulin	Endoscopically resolved
Tahan et al.**(32)**	Gastric and Small Bowel 40M	Common variable immune deficiency (CVID)	6-month history of abdominal pain, 10kg LOW with SBO	Inflammation NQ, intranuclear inclusions, IHC +	Ganciclovir 56 days	Clinically resolved
Maiorana et al.**(33)**	Colon 84F	NIL	1-week abdominal pain, diarrhea, fevers	Inflammation NQ, intranuclear inclusions, IHC +	Ganciclovir 14 days	Clinically resolved
Maiorana et al.**(33)**	Colon 67M	NIL	5 days abdominal pain, diarrhea, fever	Inflammation NQ, intranuclear inclusions, CMV IHC +, CMV PCR on tissue positive	Ganciclovir 14 days	Clinically resolved
Farooq et al.**(34)**	Lung 70M	Severe COPD, home oxygen dependent	Identified as part of evaluation of progressive COPD	BAL: binucleate cells consistent with CMV	Valganciclovir 28 days	Clinically resolved
Agaimy et al.**(35)**	Caecum and sigmoid 70F	Renal transplant 10 years prior (sirolimus) and prior bowel cancer	Asymptomatic. Routine colonoscopy post malignancy	Intense inflammation, intranuclear inclusions, IHC +	NIL	Clinically resolved
Agaimy et al.**(35)**	Sigmoid Colon 69M	UC, MTX and sulfasalazine	Screening for UC	Intense inflammation, intranuclear inclusions, IHC +	NIL	Clinically resolved

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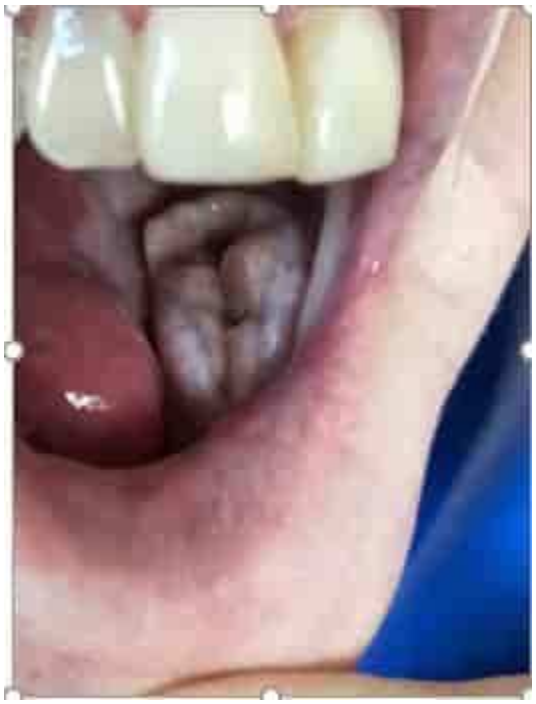
Agaimy et al.**(35)**	Colon 80F	NIL	Diarrhea	Intense inflammation, intranuclear inclusions, IHC +	NIL	Endoscopically resolved
Agaimy et al.**(35)**	Stomach 56M	NIL	pain	Intense inflammation, intranuclear inclusions, IHC +	NIL	Endoscopically resolved
Karakelides et al.**(36)**	Lung 49M	NIL	6 weeks of left shoulder pain and productive cough	Inflammation NQ, intranuclear inclusions, IHC +	NIL	Clinically resolved
Imam et al.**(37)**	Colon 60F	Renal transplant 1 year prior (CMV +/-) (CyA + sirolimus + prednisolone) and prior bowel cancer with partial colectomy	1 week of bloody diarrhea and bilious vomiting	Inflammation NQ, intranuclear inclusions, IHC +	Ganciclovir for unclear duration	Endoscopically resolved
Lewis-Jones et al.**(38)**	Colon 53M	Renal transplant 9 years prior (Aza + prednisolone)	8 months of intermitted epigastric pain with 2 months diarrhea	Inflammation NQ, intranuclear inclusions, IHC +	NIL	Clinically resolved
Diaz-Gonzalez et al.**(39)**	Colon 57F	14 months post orthoptopic heart transplant (CMV +/+), CyA + Aza	24 hours of intermittent crampy abdominal pain, diarrhea and fevers	Inflammation NQ, intranuclear inclusions, IHC ND	Ganciclovir 14 days	Clinically resolved
New	Oral 59F	pembrolizumab for recurrent SCC	3 weeks of rapidly progressive mass	Inflammation NQ, intranuclear inclusions, IHC +	Ganciclovir 28 days + valganciclovir 28 days	Clinically healing
New	Vulva 52F	Renal transplant (belatacept + MMF + prednisolone)	6 months of slowly progressive lesion with bleeding and pain	Inflammation NQ, intranuclear inclusions, IHC +	CMV immune globulin	Clinically resolved

MMF, mycophenolate; CyA, cyclosporin; AZA, azathioprine, COPD, chronic obstructive pulmonary disease; UC, ulcerative colitis; MTX, methotrexate; SCC, squamous cell carcinoma; ICH, immunohistochemistry; Inflammation NQ, inflammation not quantified.



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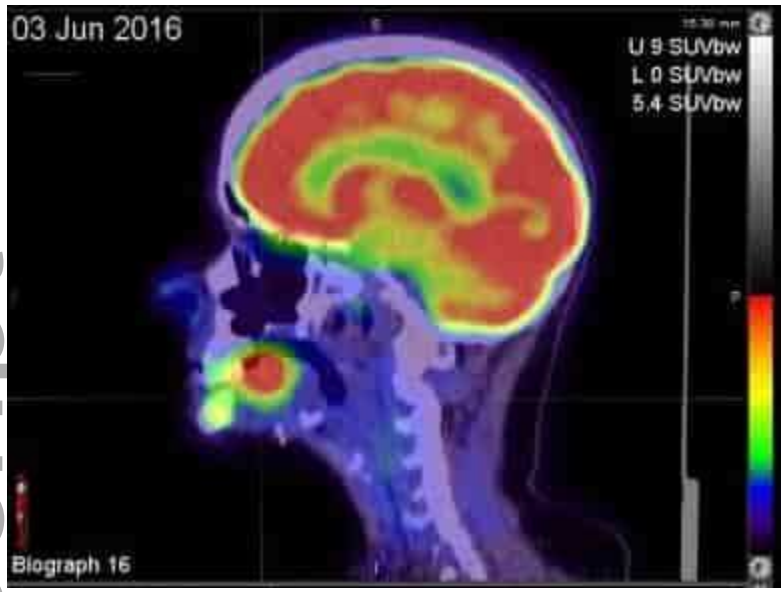

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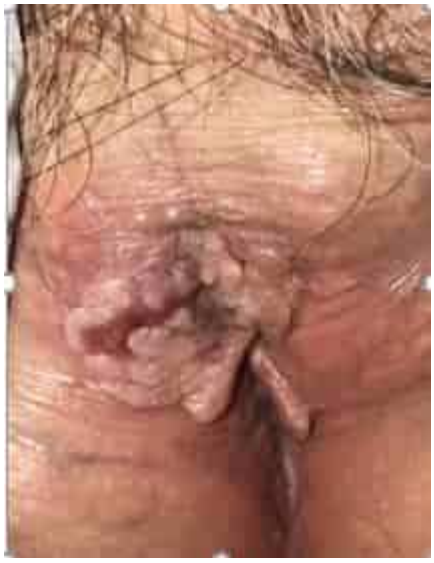

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