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Checkpoint Inhibitor Immunotherapy Related Inflammation of the Calcified Neurocysticercosis cyst

Jain V[1], Yokoda RT[2], Littig IA[3], Friedlander P[4], Kim L[5] and Germano IM[6*]

[1]Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, USA

[2]Department of Pathology, Molecular and Cell-Based Medicine, Icahn School of Medicine at Mount Sinai, New York, USA

[3]Department of Radiology, Neuroradiology Division, Icahn School of Medicine at Mount Sinai, New York, USA

[4]Department of Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, USA

[5]Department of Neurology, Neuro-Oncology Division, Icahn School of Medicine at Mount Sinai, New York, USA

[6]Department of Neurosurgery, Icahn School of Medicine at Mount Sinai, New York, USA

[*]Corresponding author:

Isabelle M. Germano,
Department of Neurosurgery, Icahn School of Medicine at Mount Sinai, The Mount Sinai Hospital, One Gustave Levy Place, New York, NY 10029, USA

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1. Abstract

Immunotherapy with checkpoint inhibitors (CPI) is successfully used to treat metastatic melanoma. Among them, ipilimumab and nivolumab are often used in combination to enhance inflammatory response, leveraging their mechanism of action on two different targets, CTLA-4 and PD-1 receptors, respectively. This, in turn, prevents the downregulation of T-cells, resulting in increased immune response to target tumor cells. While successful in melanoma and other cancer treatments, their immune response has been associated with a broad spectrum of adverse effects. We hereby report a case of CPI-associated inflammatory response on a cerebral calcified neurocysticercosis (NCC) cyst, resulting in pathological perilesional edema requiring surgical resection. Identification of increased PDL1-positivity within the NCC cyst wall of the resected lesion and increased T-cells within the surrounding brain raises the concern that CPI elicited such a response. These findings raise concern about the use of CPI in cancer patients with concurrent infectious pathology.

2. Clinical History

A 70-year-old Ecuadorian woman with history of right foot melanoma, treated with resection and radiation 2 years prior, presents for evaluation for a new onset seizure. She has a history of having calcified neurocysticercosis (NCC) cysts not requiring treatment. Her brain magnetic resonance imaging (MRI) at presentation showed two hypointense lesions in the superior temporal gyrus on the T2-weighted sequence without surrounding edema or contrast enhancement (CE) (Figure 1). These lesions correlated to previously noted calcified lesions in an outside head CT (not shown). The seizure was thought to be secondary to NCC and she was started on an anti-epileptic drug (AED) with no breakthrough seizures in the future. A surveillance staging positron emission tomography (PET) showed increased metabolic uptake in the right groin only. A biopsy was performed and the results were consistent with metastatic disease. The mass was resected and the patient was started on ipilimumab and nivolumab combination therapy for metastatic melanoma. A surveillance brain MRIeight months later showed new CE and surrounding edema of the two left superior temporal gyrus lesions. Reactivation of calcified nodular stage NCC with spontaneous development of perilesional edema is described in the literature [1]. However, in the setting of metastatic disease, evidence of newly developed edema and enhancement makes it necessary to rule out a new metastatic lesion. Distinguishing a new metastatic melanotic lesion from a calcified cyst is even more challenging as both melanotic lesions and calcified cysts are hypointense on T2-weighted imaging [2, 3].

This complex case was discussed at the institution's weekly multi-disciplinary tumor board, and unanimous consensus was to obtain tissue to confirm the diagnosis and guide further treatment. The lesions were therefore resected without any complications (Figure 1F).

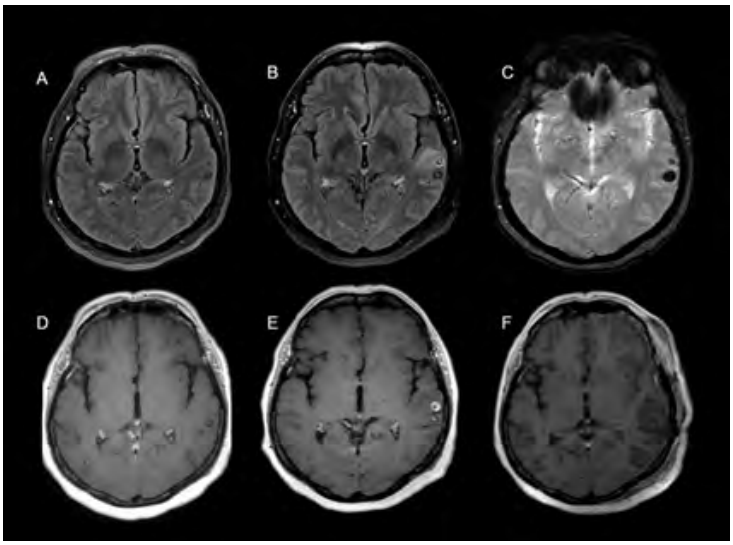

Figure 1: Axial brain MRI FLAIR and T1 post- contrast sequences at presentation **(A and D)** and eight months later on systemic ipilimumab and nivolumab for metastatic melanoma **(B and E)** showing new surrounding edema and contrast enhancement (CE) of the 2 superior temporal gyrus lesions. On Gradient echo (GRE) sequence the lesions were consistent with calcifications (C). Posto-operative MRI **(F)** showing resection of both lesions.

3. Surgical Pathology

Hematoxylin and Eosin (H&E)-stained sections showed a fibrous cystic wall with chronic inflammation, encompassing a cavity containing partially necrotic, mildly calcified debris, abundant giant cells, and cholesterol clefts consistent with a foreign body granulomatous reaction, correlated with the previous history of NCC (Figure 2A-D). The area of pericapsular neovascularization is seen (Figure 2E). Of interest, the presence of neovascularization was identified, highlighted by VEGF immunostain (Figure 2F, G), which correlated with the perilesional edema seen on MR images. An additional unexpected finding was the presence of CD3-positive T-lymphocytes were found surrounding the vessel (Figure 2H). PDL1 antibody immunostain showed partial or total membranous staining in 30% of the T cells surrounding the vessels (Figure 2J) and expression outside the necrotic areas, including in the capsule and in the brain parenchyma (Figure 2I).

After reviewing the biopsy results (as discussed above), metastatic disease was ruled out. The inflammation around the lesions was thought to be due to enhanced immune reaction from the use of combination CPI.

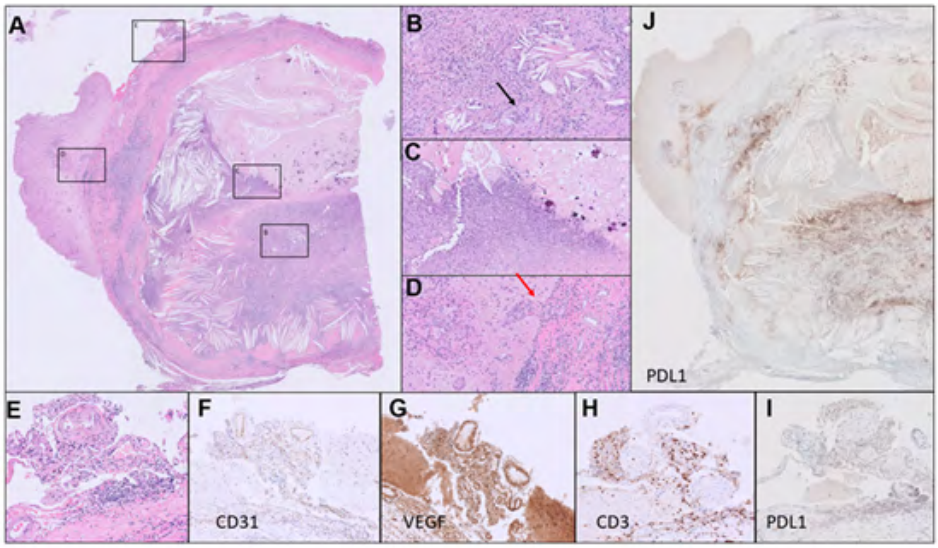

Figure 2: Microphotographs of histological slices showing **A**) Abscess wall and adjacent brain parenchyma. **B**) Cholesterol crystals and multinucleated giant cells (black arrow), characterizing granulomatous reaction. **C**) Geographic necrosis, calcifications, and ghost cells. **D**) Abscess wall with infiltrating lymphocytes, granulocytes, reactive gliosis, and neovascularization (red arrow). **E**) Area of pericapsular neovascularization showing in **F**) neovascularization positive for CD31. **G**) Neovessels positive for VEGF. **H**) CD3-positive T-lymphocytes surrounding the vessel. **I**) PDL1 antibody immunostain with partial or total membranous staining in 30% of the T cells surrounding the vessels. **J**) PDL1 low-power view showing patchy positivity with strong expression outside the necrotic areas, including in the capsule and in the brain parenchyma.

4. Discussion

4.1. Immune Checkpoints Inhibitors

Since the first FDA-approved immunotherapy in 2011, 10 additional compounds have been FDA-approved (Table 1), and various are in clinical trials [4]. Under physiological conditions, our immune system does not act against the host or self-antigen. This regulation occurs using immune checkpoints, including CTLA-4, PD-1, and PD-L1.

CTLA-4 is expressed constitutively on regulatory T cells (T-regs). Along with CTLA-4, CD28 is also present in T cells. Both receptors compete to bind to CD80/B7 on dendritic cells. Binding of CTLA-4 to CD80 sends a co-inhibitory signal to T cells, thus preventing T cell activation and proliferation. The binding of CD28 to B7 is co-stimulatory, leading to T-cell activation, proliferation, and release of cytokines. Thus, blocking CTLA-4 results in upregulation of T cell response [5].

PD-1 is a transmembrane protein predominantly expressed on memory T cells and less commonly on B cells, dendritic cells, and natural killer cells. PD-L1 is expressed in tumor cells and various other immune cells. The binding of PD-1 to PD-L1 sends an inhibitory signal preventing T cells from activating and proliferating [6]. Solid tumors tend to upregulate the expression of these checkpoints, enhance immune resistance, and escape the immune response [5]. Checkpoint inhibitors (CPI) prevent immune downregulation, result in the activation and proliferation of T cells, and release of cytokines that can target the tumor cells [7].

Table 1: FDA-approved immunotherapies

	Immunotherapy (Year of FDA approval)	***Indications***
CTLA-4	Ipilimumab (2011)	*Melanoma*
	Tremelimumab (2022)	*Hepatocellular carcinoma*
PD-1	Nivolumab (2014)	*Melanoma*
	Pembrolizumab (2014)	*Melanoma*
	Cemiplimab (2018)	*Cutaneous SCC*
	Dortarlimab (2021)	*Endometrial cancer*
	Retifanlimab (2023)	*Merkel cell carcinoma*
PDL-1	Atezolizumab (2016)	*Urothelial carcinoma*
	Avelemumab (2019)	*Merkel Cell carcinoma*
	Durvalumab (2017)	*Urothelial carcinoma*

4.2. Checkpoint Inhibitors Related Adverse Effects

Table 2 summarizes the most observed CPI-related adverse effects (CPI-r-AE). Their incidence is about 60% [8]. Cutaneous and gastrointestinal CPI-r-AE are the most common. CNS toxicities are uncommon and include encephalitis, meningitis and demyelinating encephalomyelitis [9,10]. The median onset of CPI-r-AE is around ten weeks after initiation of immunotherapy [11]. The reported incidence of CPI-r-AE is less in patients treated with anti-PD1/PDL1 alone than those treated with anti CTLA-4 or combined [11]. Table 3 summarizes the management of CPI-r-AE.

The mechanism of CPI-induced adverse effects depends on their target inhibition. CTLA-4 inhibitors, like ipilimumab, induce clonal expansion of cytotoxic T cells, elimination of Treg cells, and induction of cross-reactivity between antitumor T cells and normal healthy tissue [12]. PD1 or PDL1 inhibitors, like nivolumab, lead to a reduction of impaired Treg survival and increased cytokine production [13]. Treg cells downregulate immune response by inhibiting effector T cell proliferation; therefore, they are essential in maintaining immune tolerance. Their elimination or impaired survival leads to autoimmunity.

Normal tissues and tumor cells may share antigens, resulting in immunotherapy monoclonal antibodies to target both healthy tissues and tumor cells [14]. CPI binding to healthy tissues can result in complement activation and antibody-mediated inflammation [15]. CTLA-4 inhibitors increased the circulating Th17 cells and enhanced Th17 responses, producing pro-inflammatory cytokines like IL-17, IL-21, and IL-22, leading to inflammation [16]. CTLA-4 inhibitors increased the circulating Th17 cells. A strong correlation has been seen between early B cell subsets and the use of combination checkpoint inhibitor therapy, suggesting that B cell-mediated autoantibody production could also contribute to CPI-induced adverse effects [17].

Table 2: Common Adverse Effects of Immunotherapies

Organ-system	***Adverse effects***
Central Nervous system	Myasthenia Gravis, Guillian Barre syndrome, peripheral neuropathy, autoimmune neuropathy, aseptic meningitis, encephalitis, demyelinating disease, multiple sclerosis, transverse myelitis, autoimmune demyelinating encephalomyelitis, optic neuritis, neuromyelitis optica.
Gastrointestinal	Diarrhea, colitis, enteritis
Cardiac	Myocarditis, pericarditis, arrhythmias, impaired ventricular function, vasculitis, venous thromboembolism.
Pulmonary	Pneumonitis
Dermatological	Mucositis, alopecia areata, bullous pemphigoid, lichenoid dermatitis, pruritus, xerosis, dermatitis
Renal	Nephritis, acute kidney injury
Endocrinopathy	Hypo/hyperthyroidism, pituitary hypophysitis, diabetes
Rheumatoid Arthritis	Inflammatory Arthritis, myositis, polymyalgia
Ocular	Uveitis, Episcleritis
Hematological	Hemolytic anemia, acquired ITP, HUS, aplastic anemia, lymphopenia,

Table 3: Grading of Systemic Toxicities

Grade	**Classification**	**Clinical decision**
Grade 1	Mild transient reaction	Observation
Grade 2	Moderate	Systemic corticosteroids 0.5-1mg/kg/day prednisone
Grade 3	Severe but not immediately life-threatening	High-dose corticosteroids 1-2 mg/kg/d prednisolone or methylprednisolone
Grade 4	Life-threatening	High dose corticosteroids. Consider infliximab and rituximab in steroid-refractory cases

4.3. The Use of Checkpoint Inhibitors with Concomitant Brain Pathology

To the best of our knowledge this is the first report of use of CPI with a concomitant past medical history of NCC. Spontaneous development of edema around calcified NCC cysts has been reported (1) However, our findings showing increased neovascularization and T-cells in the NCC cyst wall, suggest that use of combined CTL4 and PD1 CPI resulted in clonal expansion of cytotoxic T cells, which targeted the cyst wall, resulting in inflammation around the cyst.

At the time of the brain MRI surveillance, the patient had completed 9 immunotherapy cycles and was neurologically asymptomatic. However, the new finding of increased edema caused challenges in the differential diagnosis prompting surgical intervention. Histopathological findings warranted the suspension of immunotherapy.

5. Conclusion

The use of combination checkpoint inhibitors immunotherapy can result in inflammation of foreign antigens like neurocysticercosis cysts in the brain. Imaging surveillance is warranted in cancer patients on immunotherapy with a dormant or latent concomitant brain pathology.

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