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Case Report

Budosenid Treatment of Avelumab Induced Autoimmune Colitis in Patient With Metastatic Merkel Cell Carcinoma; A Case Report

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ABSTRACT

Merkel cell carcinoma is a rare and highly aggressive primary cutaneous cancer with epithelial and neuroendocrine features. Currently, for stage IV disease, up-front immunotherapy with check-point inhibitors, anti PD-L1 and anti PD-1, is recommended. We report the case of a patient who was treated with Avelumab for a metastatic Merkel cell carcinoma. He presented a treatment induced grade II immune colitis, treated successfully with oral Budesonid, a synthetic steroid with high topical anti-inflammatory activity, minimal systemic absorption, and fewer side effects.

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Case Report

A 81years old male patient presented to our hospital on September 2018 with rapidly growing right cervical mass. A computed tomography (CT) of the head and neck, done in emergencies, showed a hypodense masse, 29x24mm, located at the antero-inferior part of the parotid gland (Figure 1). According to the radiologist, the most likely diagnosis was that of a cystadenolymphoma or Warthin's tumor. Our surgeon performed a surgical biopsy of this tumor and the pathology report showed cutaneous and lymph node infiltration by Merkel cell carcinoma, with deep margin invades and capsular effraction. Following this result, an FDG PET-CT was performed and this exam showed metastases in the right parotide, right cervical lymph nodes, and multiples lesions in the bones and the liver (Figure 2).

Our patient past medical history included statin induced collagen colitis treated with Budesonid in 2016, Non-ST-elevation myocardial infarction and coronary artery stenting in 2013, hypertension, dyslipidaemia, and penicillin allergy. Patient treatment at the diagnosis included cardioselective β 1-adrenergic blocking agent, ACE inhibitor, low dose aspirin, and ezetimibe, an intestinal cholesterol absorption inhibitor. We

decided to start treatment with Avelumab, a programmed death ligand-1 (PD-L1) blocking antibody. After two injections, at physical examination, the right cervical mass disappeared, suggesting response to Avelumab.

In January 2019, after three months of Avelumab treatment, the controle PET-CT scan showed complete metabolic response in all metastatic lesions, but intense and diffuse uptake in all the colon (Figure 3). The patient, who, by nature, did not speak much, told us that almost one week before his PET-CT scan he started to have grade II watery diarrhea (up to 6 times per day). No pyrexia reported. Blood test showed severe hypokalemia (K^+ 2.2U/l, with normal range between 3.5 and 4.5U/l) and acute kidney failure. CRP was minimally elevated (7.4mg/l with normal range < 5mg/l). So he was admitted to the hospital because of asthenia and deshydration. Stool culture showed no enteric pathogens. We suspected than auto-immune colitis and we performed upper and lower digestive tracts endoscopic exams. The gastroscopy was almost normal (mild gastritis), but the colonoscopy showed diffuse mucosal erythema, without ulcerations. Histological analysis of multiples colon biopsies showed intense and diffuse inflammatory infiltration, with increase in plamocytes and eosinophilic polynuclear cells. Focally, crypt abscesses

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with polynuclear neutrophils within the glandular lumen were observed (this is a non-observed characteristic in collagen colitis). No thickening of the basement membrane was observed. We compared these findings with the biopsies done in 2016 when the patient has presented the statin induced collagen colitis and we found evident differences (Figure 4-8). So the diagnosis was Avelumab induced autoimmune colitis and the check-point inhibitor was held. The patient had started supportive care, re-hydration with potassium i.v supplementation, and as he felt better and was able to swallow, we started oral Budesonid first at dose 9mg per day. Four days later we observed improvement and decrease of diarrhea to grade I. After one month we de-escalated Budesonid dose to 6mg/day, and one month later to 3mg/day and then we re-started Avelumab. At the end of April 2019, control PET-CT showed persistence of metabolic complete response of all Merkel cell carcinoma lesions, and almost normalisation of the FDG uptake in colon, which was consistent with colitis improvement (Figure 9). Currently, our patient is still continuing Avelumab with 3mgs/day maintenance dose of Budesonid, no symptoms of colitis, and excellent tolerance. He will have his next contrôle check-up in Septembre 2019, but at clinical examination there is no sign of cancer progression.

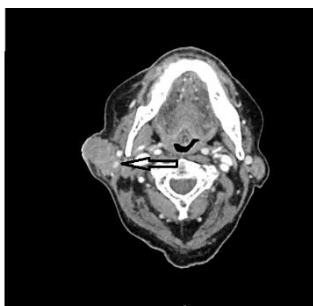


Figure 1: Cervical CT scan showing the rapidly growing large right mass.

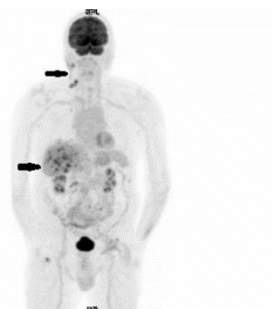


Figure 2: Base-line FDG PET-CT showing multiple right cervical lymph nodes and liver metastases.

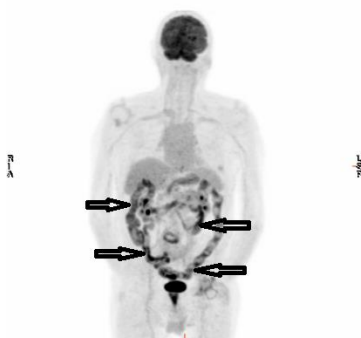


Figure 3: FDG PET-CT after the first three months of Avelumab

treatment : complete response of all Merkel cell carcinoma metastases, but intense uptake in all the colon.

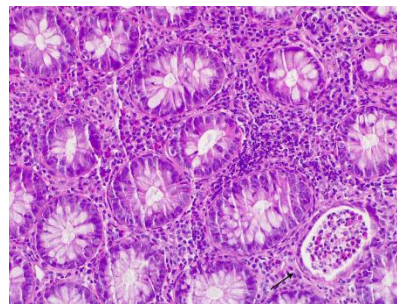


Figure 4: Colon biopsy after Avelumab induced colitis. Staining with hematoxylin and eosin (20x magnification): dense inflammatory infiltration (it was not the case for all biopsies performed in 2016) with increase in plasmacytes cells, eosinophilic polynuclear cells. Focally (arrow) we can observe crypt-abscesses with neutrophils within glandular lumen (this is non-observed in characteristic in collagen colitis).



Figure 5: Colon biopsy after Avelumab induced colitis. Staining with hematoxylin and eosin (20x magnification): no thickening of the basement membrane is observed.

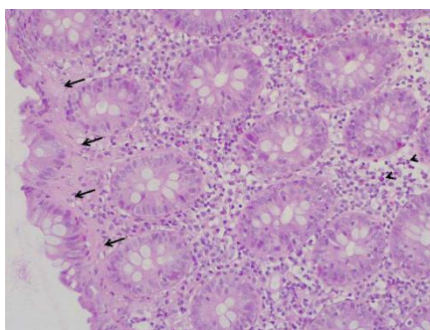


Figure 6: Colon biopsy in 2016 (collagen colitis). Staining with hematoxylin and eosin (20x magnification): collagenic thickening of the basement membrane can be observed (arrow).

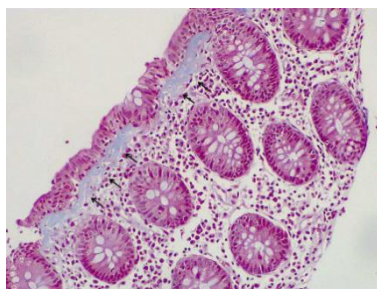


Figure 7: Colon biopsy in 2016: Masson Trichrome staining (20x

magnification): confirmation of collagenic thickening of basement membrane.

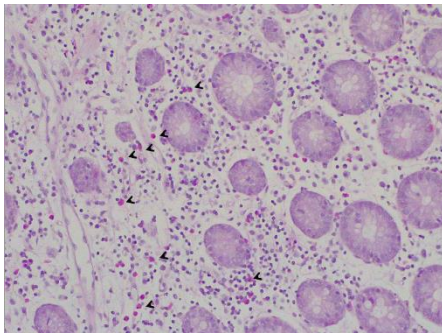


Figure 8: Colon biopsy in 2016 (collagen colitis). Staining with hematoxylin and eosin (20xmagnification) : the inflammatory infiltrate is not really increased and is composed of lymphocytes, plasmocytes, and eosinophilic polynuclear cells (arrow). These latter are too numerous.

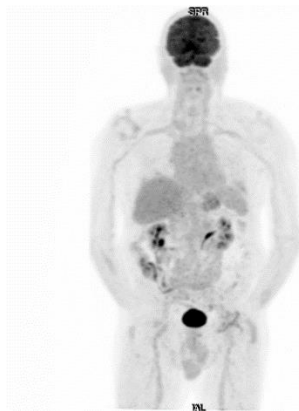


Figure 9: PET-CT done after Budesonid treatment of the Avelumab induced colitis: colon uptake normalization.

Discussion

Merkel cell carcinoma (MCC) is a rare neuroendocrine tumor of the skin, with increasing incidence over the past few decades, associated with a high risk of local recurrence and distant metastases [1]. Risk factors for MCC include age ≥ 65 years, immunosuppression, previous sun exposure, and Merkel cell polyomavirus (MCPyV) infection [2]. Until 2017, patients with advanced disease were typically treated with conventional chemotherapies, with a median response duration of 3 months. Increased evidence of the role of the immune system in controlling this cancer has paved the way for immune-based therapies, with programmed cell death protein 1 (PD-1)/programmed cell death protein ligand 1 (PD-L1) inhibitors at the frontline. Avelumab is a monoclonal anti-human PD-L1 antibody, which activates antibody-dependent cell-mediated cytotoxicity as well as blocking PD-1/PD-L1 interactions. In an international multicenter phase II trial in 88 cytotoxic chemotherapy refractory metastatic MCC patients, avelumab treatment (10 mg/kg every 2 weeks) showed ORR of 33% over the minimum follow-up period of 2 years (median 29.2 months), including a CR rate of 11% [3, 4]. In a second international, multicenter, single-arm, open-label clinical trial in 39 treatment-naïve patients, avelumab showed ORR of 62.1% at the minimum follow-up period of 3 months, including CR

of 13.8% and PR of 48.3% [5]. In 2017, based on these results, Avelumab was approved for first line treatment of patients with metastatic Merkel cell carcinoma.

Immune checkpoint inhibitors have been associated with a new subset of autoimmune-like toxicities, known as immune-related adverse events irAEs. Although the skin and colon are most commonly involved, any organ may be affected, including the liver, lungs, kidneys, and heart. The incidence of irAEs has been reported to range from 15 to 90% in late phase clinical studies [6, 7]. Gastrointestinal toxicities usually occur 6 to 7 weeks after therapy initiation and are more common with anti-CTLA-4 antibodies [8, 9]. Severe diarrhea is more common than colitis, particularly among patients receiving combination therapy or an anti-CTLA-4 agent alone. Severe colitis occurs more often with anti CTLA-4 therapy, affecting up to 7% of patients compared with 1.8% receiving antiPD-1 therapy [10-13]. Risk factors for immune checkpoint inhibitors enterocolitis include baseline microbiota composition, history of autoimmune diseases, and some data suggest the use of non-steroidal anti-inflammatory drugs [14-17].

All of the clinical guidelines recommend permanently discontinuing ICIs for grade IV colitis. For grade III colitis, recommendations vary. ASCO (American Society of Clinical Oncology) recommends considering permanent discontinuation of CTLA-4 agents, while PD-1 or PD-L1 agents may be restarted if the patient can recover to grade 1 or less. All of the societies agree that resuming ICI may be considered in grade II diarrhea once improvement is noted. For grade II ICI colitis, all guidelines recommend rehydration, ions supplementation, and administration of intravenous infusion of 1-2mg/kg/day prednisone or equivalent, [18].

We report the first case of Avelumab induced grade II colitis treated successfully with oral Budesonid, a synthetic steroid with high topical anti-inflammatory activity, minimal systemic absorption, and fewer side effects. Budesonid affinity for glucocorticoid receptors is 195 times greater than hydrocortisone and 15 times greater than prednisolone [19, 20]. Five milligrams of Budesonid is therapeutically equivalent to 12mg prednisolone [21]. Its rapid elimination, thanks to a 90% first-pass hepatic metabolism, results in a low systemic bioavailability which reduces its adverse effects. Its metabolites are mainly excreted in the urine, and, to a lesser extent, in the faeces [22]. Budesonide's efficacy in treating microscopic colitis in both histological forms, collagenous colitis, and lymphocytic colitis, has been demonstrated in several reviews and in the European Consensus [19, 20]. Compared with systemic glucocorticoids, oral budesonide has a markedly reduced effect on endogenous cortisol production, and expert recommendations do not consider dose tapering before discontinuation to be necessary [23-29]. This has an important safety aspect especially in elderly patients. In conclusion, we report a case of moderate, grade II anti-PD1/PDL-1 induced immune colitis treated successfully with oral Budesonid, a second generation steroid, with strong topical activity, and safer toxicity profile. We suggest that this therapy could be proposed for this category of patients.

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