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Case Report

Aggressive Behaviour of Merkel Cell Carcinoma in a Kidney Transplant Patient Receiving Tacrolimus Treatment – Is There an Alternative in Immune Checkpoint Inhibitor Treatment?

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ABSTRACT

Background: Merkel cell carcinoma (MCC) is a rare skin neoplasm first described by Toker in 1972. The tumor usually presents in the sixth to seventh decade of life as a solitary reddish-brown to violaceous subcutaneous nodule on the head, neck, or the extremities. It is seen at an earlier age only in immunocompromised patients like transplant patients in immunosuppressive therapy. Thus, cancer has now become the second cause of death among transplant patients. The tumor growth is rapid in MCC patients, and for metastatic disease, no substantial benefit is obtained by chemotherapy. A new drug has recently become available, an immune checkpoint inhibitor (CPI), avelumab, that is able to delay disease progression significantly. However, there are no current guidelines for the use of immune checkpoint inhibitors in transplant patients.

Case Presentation: We describe the case of a 55-year-old kidney transplant patient on immunosuppressive therapy with tacrolimus with an early occurrence of a Merkel cell carcinoma whose aggressive behaviour could not be hampered by Avelumab, due to fear of allograft rejection.

Conclusion: CPI therapy is potentially lifesaving in advanced MCC. Further studies are urgently needed to test its benefit in this rapidly expanding field of post-transplant malignancies where there are only a few and less effective therapeutic options.

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Background

MCC is a rare skin neoplasm. Since its first description in 1972, approximately 650 cases have been documented with an estimated incidence of 0.16 per 100,000 persons [1-3]. The tumor grows in areas of skin exposed to the sun and usually presents in the sixth to seventh decade as a solitary reddish-brown to violaceous subcutaneous nodule on the head, neck, or the extremities. Histologically, MCC is characterized by a dermal infiltrate of small round cells that are uniform in size with round to oval nuclei and scanty cytoplasm. Immunohistochemistry identifies the cells as staining positive for

neuron-specific enolase (NSE), low molecular weight keratin, and chromogranin G, and negative for S-100 and LCA-45. MCC is an aggressive tumor and has a high propensity to recur locally and to metastasize to regional and distal lymph nodes.

The prognosis is very poor; besides the successful management of locoregional disease, the benefit of systemic treatment in the metastatic setting has not been demonstrated [2, 3]. MCC is seen at an earlier age only in immunocompromised patients like a transplanted patient in immunosuppressive therapy. Solid organ transplant recipients have a higher risk of neoplastic complications because of immunosuppressive treatments and oncogenic viral infections. Thus, cancer has now become

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the second cause of death among transplanted patients [4-6]. The tumor growth is also rapid in these patients, and for metastatic disease, no substantial benefit is obtained by chemotherapy. Immune checkpoint inhibitors (CPIs) have opened a new era in the treatment of cancer, and their indications are increasing rapidly. To date, these CPIs include anti-CTLA-4 (ipilimumab), anti-Programmed Death 1 (PD-1) (nivolumab, pembrolizumab) and anti-Programmed Death-Ligand 1 (PD-L1) (atezolizumab, avelumab, durvalumab) antibodies [7]. One of these CPIs, avelumab, is able to delay disease progression in MCC significantly [8].

However, data are lacking regarding the use of CPIs in transplanted patients because they were excluded from clinical trials for the theoretical risk of organ rejection. Only a few isolated cases of CPIs use in transplant recipients have been reported in the literature so far [9]. Therefore, although there is a clear medical need, the feasibility of these new therapies in transplanted patients with cancer has not been proved yet. After the publication of encouraging PFS prolongation induced by avelumab, an anti-PD-1 inhibitor, in advanced Merkel cell carcinoma in immunocompetent patients, some authors have employed CPIs in transplanted patients and have demonstrated that the risk of allograft rejection, intrinsic to all CPIs, may be counterbalanced by encouraging results in terms of the control of the metastatic disease [8]. Lesouhaitier *et al.* reported a retrospective analysis of seven kidney transplant patients with cancer treated with CPIs.

The authors hypothesize that there are some factors that affect the safety of immunotherapy in transplanted patients that include the integral role of the PD-1 pathway compared with the CTLA-4 pathway in organ acceptance, sequential implementation of different CPI classes, length of time from the transplant before immunotherapy, the strength of immunosuppressive agents to prevent organ transplant rejection, and immunogenicity of the particular organs grafted. Although limited cases have been reported, there are circumstances in which CPIs have been used in transplanted patients without resulting in organ rejection. It seems that allograft rejection is less likely to occur with anti-CTLA-4 agents if compared to anti-PD-1 drugs [10, 11]. A recent review confirms the efficacy and tolerance of CPIs in transplant patients with cancer [12].

Case Presentation

We report here, the history of a 55-year-old man affected by a neuroendocrine Merkel cell carcinoma of the left cheek treated with surgery and radiotherapy, metastatic to the nodes and liver. The patient had received left kidney transplantation, in 2012, for chronic renal failure secondary to post-nephritic syndrome, and was taking long term tacrolimus 0.5 mg 1+1/2 cp twice daily and micofenolato 7.6 mg twice daily as an immunosuppressant treatment to avoid allograft rejection. In 2014 he had suffered an ischemic stroke and in 2017 an acute myocardial infarction treated with percutaneous transluminal coronary angioplasty with the deployment of 2 stents. Previous dorsal herpes zoster, dyslipidemia, osteopenia, previous dialysis for post-nephritic renal failure, are registered in his clinical history.

Six years after the kidney transplant, in January 2018, he showed a nodular cutaneous neoplastic lesion of 30 mm of diameter on the back of the nose treated with a surgical excision. The histological pattern was

that of an ulcerated basal cell carcinoma radically excised. After seven months, in July 2018, he was subjected to a further surgical excision of a reddish cutaneous mass sized 20 mm on the left side of the nose. The histology documented a trabecular Merkel cell carcinoma. The immunohistochemistry showed CK pool positivity, synaptophysin positivity and a Ki 67 value of 70%. After three months, a cutaneous relapse was clinically evident and surgically removed. The histologic examination confirmed the MCC with the involvement of lateral and deep resection margins. In the meantime, a computed tomographic (CT) examination showed the new appearance of pathological submandibular lymph nodes sized 20 mm of diameter. At the clinical examination, a voluminous (bulky) local relapse of skin disease involving the nose and the contiguous left cheek and a discromic flat lesion in the left eyebrow suggestive of basal cell carcinoma were also evident.

In September 2018, for the extension of the rapidly growing disease, the patient was subjected to external photons radiotherapy for 30 days with a total dose on left cheek and neck nodes of 5400 and 6600 Gy respectively, with good local control of disease. After five months, on February 2019, he was again submitted to the excision of a skin local relapse. Then the patient underwent workup with CT body that did not show evidence of metastatic spread. In June 2019, after only four months from the last surgical treatment, a clinical examination showed three new skin lesions that were radically excised, and a CT scan showed the new appearance of multiple liver and thoracic nodal secondary lesions.

In this setting, CPI treatment would have represented the best therapeutic option for the patient, but he was ineligible for the administration of the approved drug, Avelumab, due to his poor renal function, his concomitant immunosuppressive treatment and the secondary multifactorial anemia.

Moreover, the patient was reluctant to receive a treatment that could potentially induce kidney rejection. After a multidisciplinary meeting and also considering the patient's wishes, we started treatment with personalized oral etoposide chemotherapy, but after three months, a CT examination documented increased size of secondary liver lesions, the new appearance of minimal abdominal and thoracic effusion, multiple thoracic and abdominal secondary nodal enlargement. A local recurrence of cutaneous lesion localized in the left cheek was also seen. The worsening of renal function with a serum creatinine of 2.90 mg/dl (n.v. 0.72-1.18), and a creatinine clearance of 28 ml/min (n.v. 71-151) required the withdrawal of the etoposide treatment. We decided for a no standardized approach consisting of weekly intravenous vincristine at the dose of 1.5 mg/m². From January 2020, after a clinical and CT documentation of progressive disease of soft tissues, he was submitted to palliative radiotherapy of a painful right-hand subcutaneous lesion and to the best supportive care for the rapid worsening of the general and clinical conditions.

Discussion

Solid organ transplant patients have an increased risk of neoplasms like epithelial and non-epithelial cancer due to immunosuppressive concomitant treatments. The most common tumors reported in transplanted patients are skin basal or squamous cell carcinomas, Merkel cell carcinoma and non-Hodgkin's lymphoma [4-6]. Frequently these

tumors are more aggressive if compared to similar cases in no transplant patients. MCC is a rare tumor, and like other rare tumors, it has a worse prognosis because of paucity of medical treatments and of intrinsic aggressiveness of histologic cell type that showed high mitotic index and strong metastatic spread. For immunocompetent patients with MCC, the prognosis is poor, but it is even worse in transplant patients, suggesting the need for an intensive skin examination in these patients in order to obtain early diagnosis and, hopefully, radical excision of lesions [13].

In immunocompromised patients, MCC appears almost 20 years earlier than in immunocompetent patients, with a mean age of 50 years at the onset of the disease [4-6]. When the diagnosis of cancer is made, we think that it is also mandatory to establish what is the best immunosuppressive maintenance treatment considering the difficult management of related side effects [14]. Actually, there is no complete agreement of guidelines (KDIGO) about dose and possible association of 2-3 drug combinations as cyclosporin or tacrolimus/antimetabolite (azathioprine, MMF or EC-MPS)/steroids. In fact, although the data about the incidence and behavior are often lacking due to the rarity of the disease, for patients with metastatic disease, the treatment of choice would be Avelumab. However, this drug, like other PD-1 inhibitors, is associated with a high risk of transplant rejections that make it unsuitable for life-dependent transplant patients.

Previous literature data have tried to explain the mechanisms of action of CPI-induced allograft rejection in organ transplant patients. It is possible that CPIs interact with intrarenal T-cells that can eventually cause inflammation confined to the kidney. Additionally, intrarenal T cells induce the production of autoantibodies (anti-DNA) or inhibit T-reg; both mechanisms may further increase the proliferation of autoreactive T-cells with selective tropism to the kidneys. Interestingly, this T-cell response to kidney allograft antigens can be downregulated by the expression of PD-L1 on the tubular epithelium of the kidney [12]. Thus, PD-L1 expression patterns on renal allografts may determine the risk of rejection due to PD-1 inhibitors. But, unfortunately, data on the connection between the expression patterns of PD-L1 and the risk of allograft rejection are very scarce. As far as anti-CTLA-4 therapy is concerned, further investigations are needed to confirm that these drugs have the lowest allograft rejection potential among CPI drugs, as shown in some studies, and that they are better suited for transplant patients [12].

For early metastatic MCC, we think that is mandatory to establish clinical guideline about the management of immunosuppressive agents in order to minimize the risk of their long-term toxicity. It is also necessary to investigate the etiologic and prognostic role of concomitant infections like HPV-related disease; so far, only few and conflicting data about this topic are available. HPV and its aggressive variants play a key role for many neoplastic diseases, like anal cancer, head & neck cancer and lately, cervical cancer where its presence may affect the prognosis and treatment of patients [15]. Immunodeficiency-related risk factors as ultraviolet-induced immunosuppression, organ transplantation, HIV diseases and immune disease may have a pivotal role in transplant patients as well, and they may also explain the earlier onset of MCC in these patients if compared to the immunocompetent general population.

Conclusion

CPI therapy is potentially lifesaving in MCC. Further studies are urgently needed to test its therapeutic benefit in this expanding group of post-transplant malignancies in which there are very few and less effective therapeutic options. The goal is to find a single drug with the lowest allograft rejection propensity among CPI drugs.

In the meantime, we also need to find a novel biologic marker to “grade” the immunocompetent “status” of the patients to predict the impact of immunotherapy. With a targeted CPI and an “immunocompetency” evaluation of the transplant patients, we will not deny, hopefully in a near future, a potentially useful treatment like immunotherapy in these patients with unique and so far unmet needs.

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