represents an alternative for the antirejection maintenance therapy. Furthermore, they can have a role in the treatment of Kaposi's sarcoma, since they also decrease the production of VEGF and inhibit the response of vascular endothelial cells to stimulation by VEGF. Therefore, mTOR inhibitors, not only inhibit the growth of certain vascularized tumors, while maintaining a lower risk of losing the renal graft.[6]

In the present case the patient presented only with a cutaneous lesion due to Kaposi Sarcoma, that resolved with the switch from tacrolimus to everolimus. This fact supports that mTOR inhibitors represent an alternative that allows the preservation of the renal graft, while treating Kaposi sarcoma.

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Advanced Cutaneous Squamous Cell Carcinoma Treated with Pembrolizumab☆

Carcinoma epidermoide cutáneo avanzado tratado con pembrolizumab

To the Editor:

Cutaneous squamous cell carcinoma (CSCC) metastatic to lymph nodes is an entity with low incidence (2.4% in males and 1.1% in females), which often poses a therapeutic challenge. Traditionally, systemic treatment of nonresectable cases has involved platinum-based antineoplastic drugs and epidermal growth-factor inhibitors, with or without radiation therapy. Recent studies, however, increasingly point to immune checkpoint inhibitors as the most effective and safe alternative for treatment of locally advanced or metastatic disease. We report the case of a patient with CSCC metastatic to the lymph nodes, who showed a complete objective response after 6 months of treatment with pembrolizumab.

The patient was an 83-year-old woman who was treated for moderately differentiated and infiltrating CSCC with a thickness of 8 mm, with no lymph-vessel or perineural involvement and spared margins, in the right mandibular ramus. Expression of programmed cell death ligand (PD-L1) was 30% in cancerous cells. The patient's personal history included a diagnosis of invasive ductal carcinoma that did not progress and was not treated. Three months after the intervention, the patient developed a metastatic conglomerate lymph-node mass in the angle of the right side of the jaw, measuring 4.5 cm; the mass was confirmed to be squamous cell carcinoma by means of fine-needle aspiration cytology. Curative radiation therapy was performed but the lymph-node disease progressed and an anterior cervical mass measuring up to 8 cm developed. In light of the nonresectable nature of the disease and its progression despite radiation therapy, with an ECOG score of 0, permission was sought for off-label use of pembrolizumab. The patient began treatment with pembrolizumab at a dosage of 2 mg/kg every 3 weeks, with rapid reduction in tumor size after 4 cycles and complete clinical and radiologic remission maintained over 6 (Figs. 1 and 2). The treatment was well tolerated, and the patient presented only a syndrome similar to rheumatic polymyalgia, which remitted with analgesics and 200 mg of hydroxychloroquine every 12 hours. At the same time, the ductal carcinoma showed no alternations in the control mammograms.

The role of immunotherapy in skin cancer is becoming increasingly important. PD-1 inhibitors are producing highly promising results for the treatment of locally advanced and metastatic CSCC,[1–5] with a response rate of up to 60% according to the latest reviews - mostly in the form of partial responses.[4] Cemiplimab, a programmed cell death receptor 1 (PD-1) antibody, has recently been approved with indications by the EMA and the FDA for locally advanced CSCC. Pembrolizumab is an anti-PD-1 monoclonal antibody indicated as adjuvant treatment in resected stage III melanoma, advanced melanoma, Hodgkin lymphoma, urothelial carcinoma, non-small cell lung cancer, and squamous cell carcinoma of the head and neck. Its mechanism of action affects the immunological synapse, inhibiting the coinhibitory activity of PD-1, thus favoring destruction of the tumor by intratumoral CD8 T cells.[6] Studies exist on the expression of PD-1 and PD-L1, and on the type of intratumoral inflammatory infiltrate and its relation to tumor characteristics[7] and treatment response.[8]

It is not clear that a cutoff exists in the expression of PD-1 and PD-L1 in CSCC tumor cells and its relation to the response to anti-PD-1 drugs, although a positive correlation appears to exist.[7,8] Similarly, expression of PD-L1 has also been linked to high-risk characteristics such as the infiltration pattern, perineural invasion, and immunosuppression.[7] To date, most publish results are of partial responses,[4] although

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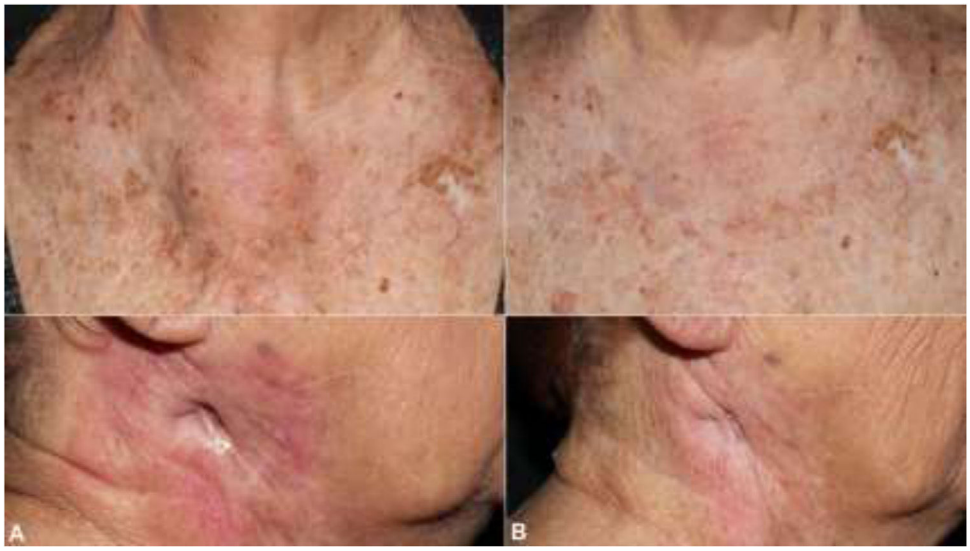

Figure 1 Clinical image of the presternal tumor and the angle of the right side of the jaw before (A) and after (B) 4 cycles of pembrolizumab. Closure of the tumor fistula in the angle of the right side of the jaw after treatment can be seen (B, bottom).

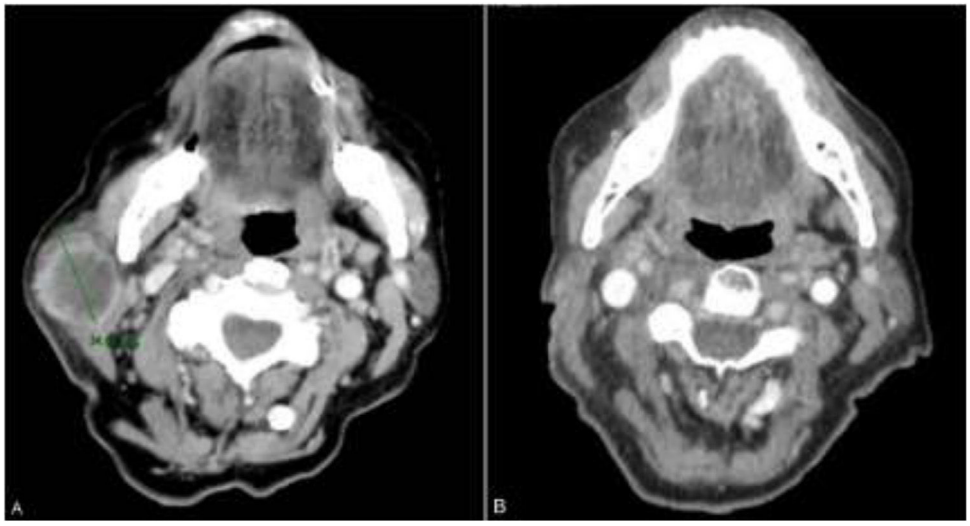

Figure 2 Computed tomography image of the tumor on the right side of the jaw before (A) and after (B) 4 cycles of pembrolizumab.

complete responses have also been reported (Table1); the time for which treatment should be maintained is therefore not clear.[1–3] Nevertheless, this is a treatment with a good safety profile, which is especially important given that it is used mostly in elderly patients.[4,9] Immune-mediated adverse effects may appear during treatment or even months after treatment has been suspended. The most frequent of these are cutaneous adverse effects, followed by colitis, hepatitis, endocrinologic effects, pneumonitis, and arthritis.[10] In general, immune-mediated adverse effects tend to be mild (grade 1–2), and can be managed in an outpatient setting with oral corticosteroid dosages of 0.5–1 mg/kg/d of prednisone. More severe cases (grade 3) require admission to hospital, temporary suspension of the immunotherapy, and treatment with intravenous systemic corticosteroids at dosages of between 1 and 2 mg/kg/d; immunosuppressive therapy should be considered if no response is achieved after 48–72 hours.[10] We report a case of locally advanced CSCC in an elderly patient, with complete response following treatment with pembrolizumab as first-line systemic treatment.

Table 1 Review of cases of advanced squamous cell carcinoma treated with anti-PD1 in the literature.

Reference	Age and sex	Tumor	Drug	Cycles	Response	Progression-free interval
Chang, 2016	70, M	LA-CSCC	Pembrolizumab	6	CR	5 mo
Borradori, 2016	79, M	M-CSCC	Pembrolizumab	NS	PR	7 mo
	65, F	LA-CSCC	Pembrolizumab	NS	NS	4 mo
	61, F	LA-CSCC	Nivolumab	NS	PR	7 mo
	66, F	M-CSCC	Nivolumab	NS	PR	6 mo
Winkler, 2017	74, F	LA-CSCC	Pembrolizumab	4	PR	5 mo
Lipson, 2016	54, F	M-CSCC	Pembrolizumab	NS	PR	NS
Stevenson, 2017	70, M	LA-CSCC	Pembrolizumab	4	CR	11 mo
Sellah, 2018	81, M	LA-CSCC	Nivolumab	8	CR	10 mo
	41, M	LA-CSCC	Nivolumab	8	CR	5 mo
	83, M	LA-CSCC	Nivolumab	4	PR	2 mo
Degache, 2017	80, M	LA-CSCC	Pembrolizumab	>6	PR	NS
	76, M	LA-CSCC	Pembrolizumab	>3	PR	NS
Ravulapati, 2017	74, M	LA-CSCC	Pembrolizumab	7	CR	5
Delein, 2017	48, F	M-CSCC	Pembrolizumab	>3	PR	>3 mo
Blum, 2017	66, M	LA-CSCC	Nivolumab	39	PR	2 y
	72, M	LA-CSCC	Nivolumab	39	CR	2 y
	81, F	LA-CSCC	Nivolumab	13	PR	12 mo
Van Baar, 2019	88, F	LA-CSCC	Pembrolizumab	4	CR	12 mo
Liu, 2019	72, M	M-CSCC	Pembrolizumab	NS	PR	16 mo
Venkatesh, 2019	56, M	LA-CSCC	Pembrolizumab	9	CR	NS
Our case	83, F	LA-CSCC	Pembrolizumab	4	CR	>3 mo

Abbreviations: LA-CSCC indicates locally advanced cutaneous squamous cell carcinoma; M-CSCC, metastatic cutaneous squamous cell carcinoma; M, male; NS, not specified; CR, complete response; PR, partial response.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Darier Disease: A Case Series of 20 Patients and Review of the Literature☆

Enfermedad de Darier: serie de 20 casos y revisión de la literatura

To the Editor:

Darier disease is a rare autosomal dominant genetic disorder that presents with reddish-brown keratotic papules in seborrheic areas as well as with palmoplantar, nail, and mucosal tissue involvement.[1] Darier disease is due to a mutation in the sarcoplasmic/endoplasmic reticulum calcium ATPase gene (*ATP2A2*), which codes for the endoplasmic reticulum ATPase calcium pump (SERCA2b).[1,2] Few case series of patients with Darier disease have been published to date.[2] We describe a series of Spanish patients with this disease in the interest of learning more about its characteristics.

To that end we searched our hospital's database to identify patients diagnosed with histologically confirmed Darier disease treated in our department between January 2008 and January 2019. We extracted the following information for the 20 cases found: age, sex, family history of Darier disease, location of lesions, and concurrent conditions (whether cutaneous or extracutaneous) (Table 1).

The patients' median age of 46 (range, 15–76) years was slightly higher than the ages reflected in the literature, where symptoms debut in patients between 12 and 20 years old; the distribution of sexes in our series was similar, however.[3] A

Table 1 Patient and Lesion Characteristics

Patient	Age, yr	Sex	Family History	Site of Skin Lesions
1	46	F	No	Skin folds (between and under the breasts, groin, behind the ear), external auditory canal, over the shin, hairline, palmoplantar pitting, dorsum of the hand
2	40	M	Mother, sister	Thorax, behind the ear, upper and lower limbs
3	17	F	Mother	Side of the neck, periumbilical region, external auditory canal, hairline, palmoplantar pitting, dorsum of the hands
4	25	M	No	Side of the neck, thorax, periumbilical region, palmoplantar pitting, dorsum of the hands
5	15	F	No	Side of the neck, thorax (between and under breasts), abdomen
6	73	F	No	Thorax (between breasts), groin, hairline,
7	76	M	No	Thorax (between breasts), periumbilical region, upper and lower limbs
8	63	F	No	Thorax (upper third), thighs, lumbar region, external auditory canal, hairline
9	74	M	No	Thorax, periumbilical region
10	23	F	No	Side of the neck, between shoulder blades
11	34	M	No	Thorax (between breasts), periumbilical region, dorsum of the hands
12	75	F	No	Thorax (between breasts), between the shoulder blades
13	30	M	No	Thorax (under the breasts), groin, side of the abdomen
14	53	F	No	Right breast (segmental)
15	34	F	Mother, grandmother	Side of the neck, thorax (under the breasts), antecubital, popliteal, lumbar region, hairline, palmoplantar pitting
16	66	F	No	Left side of the abdomen (segmental)
17	40	M	No	Side of the neck, thorax (under the breasts), lumbar region, behind the ear, palmoplantar pitting, dorsum of the hands
18	58	M	Father	Side of the neck, thorax (between and under the breasts)
19	51	F	No	Thorax (between and under breasts)
20	45	M	No	Thorax (between and under breasts), armpits

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