Resolution of refractory pruritus with aprepitant in a patient with microcystic adnexal carcinoma

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Substance P is an important neurotransmitter implicated in itch pathways.[1] After binding to its receptor, neurokinin-1 (NK-1), substance P induces release of factors including histamine, which may cause pruritus.[2] Recent literature has reported successful use of aprepitant, an NK-1 antagonist that has been approved by the US Food and Drug Administration for the treatment of chemotherapy-induced nausea and vomiting, for treatment of pruritus. We report here the case of a patient with microcystic adnexal carcinoma (MAC) who presented with refractory pruritus and who had rapid and complete resolution of itch after administration of aprepitant.

Case presentation and summary

A 73-year-old man presented with a 12-year history of a small nodule on his philtrum, which had been increasing in size. He subsequently developed upper-lip numbness and nasal induration. He complained of 2.5 months of severe, debilitating, full-body pruritus. His symptoms were refractory to treatment with prednisone, gabapentin, doxycycline, doxepin, antihistamines, and topical steroids. At the time of consultation, he was being treated with hydroxyzine and topical pramocaine lotion with minimal relief.

At initial dermatologic evaluation, his tumor involved the lower two-thirds of the nose and entire upper cutaneous lip. There was a 4-mm rolled ulcer on the nasal tip and a 1-cm exophytic, smooth nodule on the left upper lip with palpable 4-cm submandibular adenopathy (Figure). Skin examination otherwise revealed linear excoriations on the upper back with no additional primary lesions. The nodule was biopsied, and the patient was diagnosed with MAC with gross nodal involvement. Laboratory findings including serum chemistries, blood urea nitrogen, complete blood cell count, thyroid, and liver function were normal. Positron emission tomography-computed tomography (PET-CT) imaging was negative for distant metastases.

Treatment was initiated with oral aprepitant – 125 mg on day 1, 80 mg on day 2, and 80 mg on day 3 –with concomitant weekly carboplatin (AUC 1.5) and paclitaxel (30 mg/m^2) as well as radiation. Within hours after the first dose of aprepitant, the patient reported a notable cessation in his pruritus. He reported that after 5 hours, his skin "finally turned off" and over the hour that followed, he had complete resolution of symptoms. He completed chemoradiation with a significant disease response. Despite persistent MAC confined to the philtrum, he has been followed for over 2 years without recurrence of itch.

Discussion

MAC is an uncommon cutaneous malignancy of sweat and eccrine gland differentiation. In all, 700 cases of MAC have been described in the literature; a 2008 review estimated the incidence of metastasis at around 2.1%.[3] Though metastasis is exceedingly rare, the tumor is locally aggressive and there are reports of invasion into the muscle, perichondrium, periosteum, bone marrow, as well as perineural spaces and vascular adventitia.[4]

The clinical presentation of MAC includes smooth, flesh-colored or yellow papules, nodules, or plaques.[3] Patients often present with numbness, par-

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esthesia, and burning in the area of involvement because of neural infiltration with tumor. Despite the rarity of MAC, pruritus has been reported as a presenting symptom in 1 other case in the literature.[4] Our case represents the first report of MAC presenting with a grossly enlarging centrofacial mass, lymph node involvement, and severe full-body pruritus. Our patient responded completely, and within hours, to treatment with aprepitant after experiencing months of failure with conventional antipruritus treatments and without recurrence in symptoms in more than 2 years of follow-up.

Aprepitant blocks the binding of substance P to its receptor NK-1 and has been approved as an anti-emetic for chemotherapy patients. Substance P has been shown to be important in both nausea and itch pathways. The largest prospective study to date on aprepitant for the indication of pruritus in 45 patients with metastatic solid tumors demonstrated a 91% response rate, defined by >50% reduction in pruritus intensity, and 13% recurrence rate that occurred at a median of 7 weeks after initial treatment.[5] Aprepitant treatment has been used with success for pruritus associated with both malignant and nonmalignant conditions in at least 74 patients,[6] among whom the malignant conditions included cutaneous T-cell lymphoma, Hodgkin lymphoma, and metastatic solid tumors.[5-7] Aprepitant has also been used for erlotinib- and nivolumab-induced pruritus in non–small cell lung cancer, which suggests a possible future role for aprepitant in the treatment of pruritus secondary to novel cancer therapies, perhaps including immune checkpoint inhibitors.[8-10]

However, despite those reports, and likely owing to the multifactorial nature of pruritus, aprepitant is not universally effective. Mechanisms of malignancy-associated itch are yet to be elucidated, and optimal patient selection for aprepitant use needs to be determined. However, our patient's notable response supports the increasing evidence that substance P is a key mediator of pruritus and that disruption of binding to its receptor may result in significant improvement in symptoms in certain patients. It remains to be seen whether the cell type or the tendency toward neural invasion plays a role. Large, randomized studies are needed to guide patient selection and confirm the findings reported here and in the literature, with careful documentation of and close attention paid to timing of pruritus relief and improvement in patient quality of life. Aprepitant might be an important therapeutic tool for refractory, malignancy-associated pruritus, in which patient quality of life is especially critical.

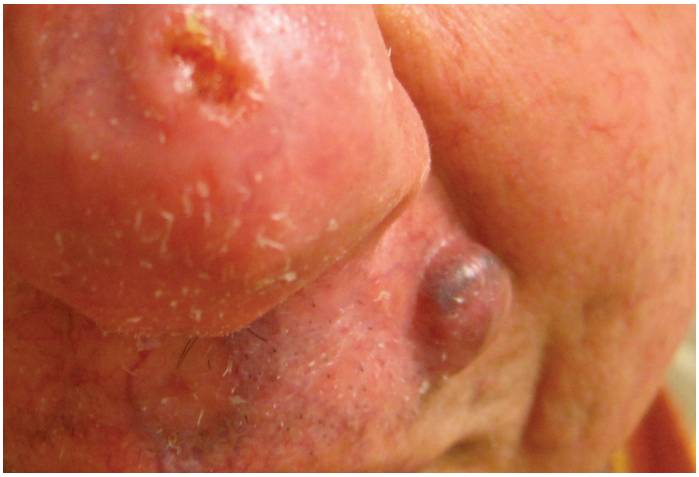

FIGURE Microcystic adnexal carcinoma: centrofacial mass infiltrating the lower two-thirds of the nose, philtrum and entire upper lip.

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