Pemphigus vulgaris (PV) is a rare (incidence: 0.5–1/100,000 inhabitants) and severe autoimmune bullous skin disease with a frequency peak between the 40th and 60th year of life (1). Two thirds of patients have painful erosions in the oral mucosa; less frequently the genital mucosa, the conjunctiva, the larynx and the esophagus are affected (1). In the following we report about a patient with human papilloma virus (HPV)-positive squamous cell carcinoma (SCC) of the oropharynx arising in PV.

**CASE REPORT**

We report on a 69-year-old patient with an initial diagnosis of PV (in ELISA: desmoglein 3 antibody positive). At the beginning, the patient showed multiple isolated erosions of the buccal mucosa, the palate and the tongue as well as isolated small erosions on the capillitium, in the face and on the back. The course of the Pemphigus Disease Area Index (PDAI, active lesions) is shown in Fig. 1A. The PDAI was recorded retrospectively on the basis of the photo documentation during subsequent in-patient treatment. He had been a smoker until the age of 28 (10 pack years).

The patient received immunosuppressive therapy with prednisolone (initially with 1 mg/kg/body weight (bw), mainly low-dose 5–7.5 mg/day) and sequentially with azathioprine (150 mg/day), mycophenolate mofetil (2.5 g/day), cyclophosphamide (2 cycles, cumulative dose 3.6 g), immunoadsorption (42 cycles), rituximab and intravenous immunoglobulins (IVIG) (20–25 mg/day) resulting in a chronic recurrent course and partial remission (Fig. 1A). The combination of rituximab and IVIG was given according to the study scheme of Ahmed et al. (2) for patients with refractory PV (induction therapy: two cycles of rituximab (375 mg/m²) once weekly for 3 weeks and IVIG (2 g/kg/bw) in the 4th week, followed by a monthly infusion of rituximab and IVIG for 4 months). Local findings were regularly monitored by ENT (ears, nose and throat) physicians and by imaging. Eight years after the initial diagnosis of PV, the patient reported increased swallowing difficulties during therapy with IVIG and mycophenolate mofetil. Multiple erosions in the pharynx, soft and hard palate were locally visible (Fig. 1B). A mirror examination of the oropharynx revealed a suspected malignant degeneration.

A biopsy (squamous epithelium with papillary proliferation with high-grade intraepithelial neoplasia/dysplasia) (Fig. 1C) and MRI revealed a poorly differentiated SCC of the oropharynx, cT3 cN0 cM0, HPV 16 – positive.

Primary radiotherapy was performed for 5 weeks (70 Gy, ED: 2 Gy). In parallel, PV therapy with IVIG, low-dose prednisolone and supportive artificial nutrition was continued, and mycophenolate mofetil was terminated. After 8 months, local examination showed a clear reduction of enoral erosions. Mirror examinations of the oropharynx no longer showed any evidence of a tumor (Fig. 1D).

**DISCUSSION**

The development of SCC of the oropharynx in connection with PV is very rare. The development of tumors from primary acantholytic skin diseases has been reported only sporadically. One case describes the development of SCC from PV (3), one case from PV with known systemic lupus erythematosus (4), two cases from Hailey-Hailey disease (4, 5), and two cases from Darier disease (6, 7). Most cases showed predisposing factors such as sun exposure, irradiation or medication.
HPV-associated tumors in the ENT area are becoming more common (incidence in the USA 1988: 0.8/100,000 inhabitants, 2004: 2.6/100,000 inhabitants) (8). Exposure to typical risk factors such as alcohol, tobacco or poor oral hygiene is lower in patients with HPV-positive SCC of the head and neck area than in patients with HPV-negative tumors (9). There is an increased association with frequent oral sex partners and the use of marijuana (9). However, HPV-positive tumors show a better prognosis than those without HPV association (8). Again, HPV infections can be promoted by a permanent immunosuppressive state of health (e.g. HIV infections, lymphoproliferative diseases, immunosuppressive therapy) as well as by a permanently damaged epidermis with loss of epidermal barrier function in acantholytic diseases (10, 11).

Autoimmune diseases are associated with chronic inflammation, which leads to DNA damage due to oxidative stress (12) and promotes carcinoma development (13). Patients with PV were found to have a lower antioxidative capacity than healthy probands (14). The chronic course of the pemphigus inflammation in the patient presented here could therefore have favored the development of SCC. An increased expression of desmoglein 3 on mRNA level has been detected in SCC of the head and neck area. Overexpression showed a positive correlation to the invasiveness and aggressiveness of the tumor (15). It was suspected that increased expression of desmoglein 3 caused by functional disturbance of the desmosomal structure promotes tumor invasiveness, but this could not be clearly demonstrated functionally (16). It is therefore questionable whether an autoantibody mediated disorder of the desmosomal structure supports tumor spread in pemphigus patients.

There is no substantial evidence for the conclusion that HPV screening should be recommended for HPV-associated oropharyngeal SCC. However, the Center for Disease Control and Prevention (CDC) estimates that there are 34,800 cases of cancer caused by HPV infections each year and that HPV vaccinations could prevent more than 90% of them (17). Although there is no epidemiologic data which proves the prevention of HPV-associated oropharyngeal SCC through HPV vaccination, a study showed that the vaccine against HPV16/18 could prevent cervical, anal and oral HPV 16/18 infections in women (18). Persistent HPV 16 infections cause most oropharyngeal cancers. Therefore, the vaccine might – as in the case of ano-genital cancers – provide protection against HPV-associated oropharyngeal SCC (19). In conclusion, further epidemiologic investigations should be performed to evaluate a potential benefit of HPV vaccination for the prevention of HPV-associated oropharyngeal SCC.

REFERENCES

1. Kneisel A, Hertl M. Blasenbildende Autoimmundermatosen. Teil I: Klinik. J Dtsch Dermatol Ges 2011; 9: 844–859.
2. Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. N Engl J Med 2006; 355: 1772–1779.
3. Mahomed Y, Mandel MA, Cramer SF, Michel B. Squamous cell carcinoma arising in pemphigus vulgaris during immunosuppressive therapy. Cancer 1980; 46: 1374–1377.
4. Bifulco G, Mandato VD, Piccoli R, Giampaolino P, Mignonna C, Mignonna MD, et al. Early invasive vulvar squamous cell carcinoma arising in a woman with vulvar pemphigus vulgaris and systemic lupus erythematosus. BMC Cancer 2010; 10: 324.
5. Felbert V, von Hampl M, Talhari C, Engers R, Megahed M. Squamous cell carcinoma arising from a localized vulval lesion of Hailey-Hailey disease after tacrolimus therapy. Am J Obstet Gynecol 2010; 203: e5–7.
6. Latour DL, Amonette R, Bale GF. Darier’s disease associated with cutaneous malignancies. Dermatol Surg Oncol 1981; 7: 408–412.
7. Orihuela E, Tyring SK, Powell M, Dozier S, Cirelli R, Arany I, et al. Development of human papillomavirus type 16 associated squamous cell carcinoma of the scrotum in a patient with Darier’s disease treated with systemic isotretinoin. J Urol 1995; 153: 1940–1943.
8. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011; 29: 4294–4301.
9. Gillison ML, D’Souza G, Westra W, Sugar E, Xiao W, Begum S, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst 2008; 100: 407–420.
10. Ko M-J, Chu C-Y. Disseminated human papillomavirus type 11 infection in a patient with pemphigus vulgaris: confirmed by DNA analysis. J Acad Dermatol 2004; 51: S190–S193.
11. Ochiai T, Honda A, Morishima T, Sata T, Sakamoto H, Satoh K. Human papillomavirus types 16 and 39 in a vulval carcinoma occurring in a woman with Hailey-Hailey disease. Br J Dermatol 1999; 140: 509–513.
12. Murata M. Inflammation and cancer. Environ Health Prev Med 2018; 23: 50.
13. Bartsch H, Nair J. Chronic inflammation and oxidative stress in the genesis and perpetuation of cancer: role of lipid peroxidation, DNA damage, and repair. Langenbecks Arch Surg 2006; 391: 499–510.
14. Javanbakht MH, Djalali M, Daneshpazhooh M, Zarei M, Eshraghian MR, Derakhshanian H, et al. Evaluation of antioxidant enzyme activity and antioxidant capacity in patients with newly diagnosed pemphigus vulgaris. Clin Exp Dermatol 2015; 40: 313–317.
15. Chen Y-J, Chang JT, Lee L, Wang H-M, Liao C-T, Chiu C-C, et al. DSG3 is overexpressed in head neck cancer and is a potential molecular target for inhibition of oncogenesis. Oncogene 2007; 26: 467–476.
16. Brown L, Wasseem A, Cruz IN, Szary J, Gunic E, Mannan T, et al. Desmoglein 3 promotes cancer cell migration and invasion by regulating activator protein 1 and protein kinase C-dependent-Ezrin activation. Oncogene 2014; 33: 2363–2374.
17. HPV | HPV Cancers are Preventable | CDC; 2019 [cited 2020 Jan 19]. Available from: https://www.cdc.gov/hpv/hcp/protection-patients.html.
18. Beachler DC, Kremier AR, Schiffman M, Herrero R, Wacholder S, Rodriguez AC, et al. Multisite HPV16/18 vaccine efficacy against cervical, anal, and oral HPV infection. J Natl Cancer Inst 2016; 108.
19. Sheedy T, Heaton C. HPV-associated oropharyngeal cancer. JAAPA 2019; 32: 26–31.