Human Papilloma Virus-positive Squamous Cell Carcinoma of the Oropharynx Arising in Pemphigus Vulgaris

Sophia LEHR, Stefanie HEYNE, Katja BERNDT, Stefan BEISSERT, Susanne ABRAHAM and Claudia GÜNTHER
Department of Dermatology, University Hospital Dresden, DE-01307 Dresden, Germany. E-mail: sophia.schneiderat@uniklinikum-dresden.de
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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. 1**A. 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/m^2) 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.

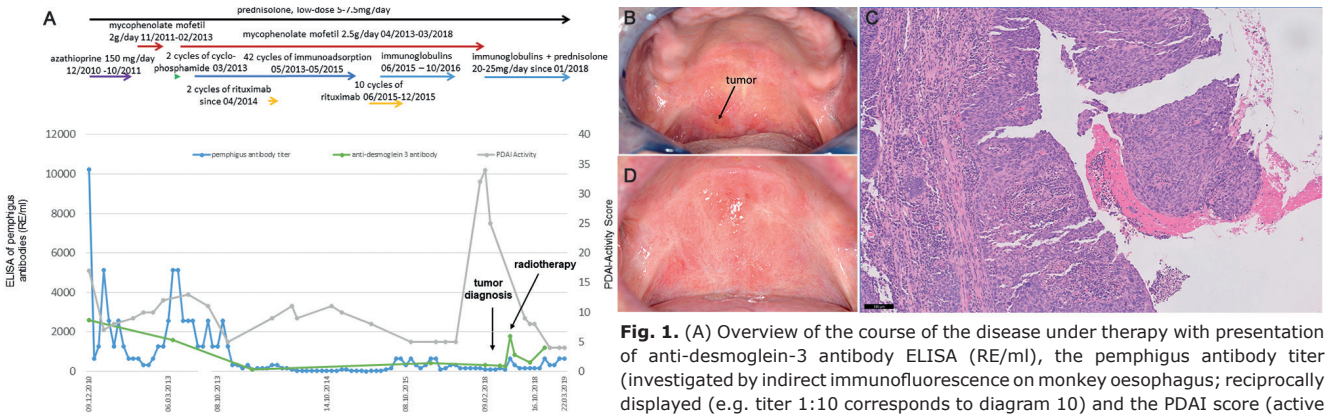

Fig. 1. (A) Overview of the course of the disease under therapy with presentation of anti-desmoglein-3 antibody ELISA (RE/ml), the pemphigus antibody titer (investigated by indirect immunofluorescence on monkey oesophagus; reciprocally displayed (e.g. titer 1:10 corresponds to diagram 10) and the PDAI score (active lesions); (B) Multiple erosions in the pharynx, soft and hard palate at the time of initial diagnosis of the poorly differentiated squamous cell carcinoma (SCC) of the oropharynx; (C) Histology of skin biopsy of the SCC: squamous epithelium with papillary proliferation with high-grade intraepithelial neoplasia/dysplasia (HE staining ×10); (D) significant reduction of enoral erosions 8 months after primary radiotherapy.

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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 desmosome 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.

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