A Microcystic Adnexal Carcinoma in the Auditory Canal 15 Years after Radiotherapy of a 12-Year-Old Boy with Nasopharynx Carcinoma

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Background: Radiogenic malignancies require cure of the primary disease and a prolonged survival. The introduction of high-volt technology in the 1950s and 1960s made radical radiotherapy feasible and successful in terms of higher cure rates and longer survival. We are already in a time when a higher number of patients with radiogenic secondary malignancies must be expected.
Case Report: A 12-year-old boy is reported who suffered from an advanced nasopharynx carcinoma and was treated with radical irradiation in 1983. 15 years later he developed a rare microcystic adnexal carcinoma of the auditory canal inside the volume of the target dose. The secondary malignant neoplasm was resected and required another radiation treatment (1 Gy b.i.d.) due to involved margins.
Discussion and Literature Review: The entity of microcystic carcinoma is discussed with a review of the literature on biology, diagnosis, and treatment.

Key Words: Radiogenic malignancy · Pediatric nasopharynx carcinoma · Microcystic adnexal carcinoma · Reirradiation

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Mikrozystisches adnexales Karzinom des äußeren Gehörgangs 15 Jahre nach Radiotherapie eines 12-jährigen Patienten mit Nasopharynxkarzinom

Hintergrund: Radiogene Zweittumoren setzen Heilung der Ersterkrankung und langes Überleben voraus. Nach Einführung der Hochvolt-Strahlentherapie in den 50er und 60er Jahren wurden durch kurative Strahlentherapie höhere Heilungsraten und verlängertes Überleben ermöglicht. Wir kommen zu oder sind bereits in einer Zeit, in der mit erhöhter Wahrscheinlichkeit mit dem Auftreten radiogener Zweittumoren gerechnet werden muss.
Fallbericht: Berichtet wird über einen Patienten, der 1983 als 12-Jähriger wegen eines lokoregionär fortgeschrittenen Nasopharynxkarzinoms kurativ bestrahlt wurde und bei dem 15 Jahre später ein sehr seltenes mikrozystisches adnexales Karzinom des äußeren Gehörgangs im Volumen der Zieldosis diagnostiziert wurde. Die Zweitneoplasie wurde operiert und erforderte wegen R1-Resektion eine postoperative Radiotherapie (1 Gy b.i.d.).
Diskussion und Literaturübersicht: Die Entität des mikrozystischen Karzinoms wird mit einer Literaturübersicht in Bezug auf Biologie, Diagnose und Therapie diskutiert.

Schlüsselwörter: Radiogenes Zweitkarzinom · Pädiatrisches Nasopharynxkarzinom · Mikrozystisches Karzinom · Zweitbestrahlung

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Introduction

Parallel to the technical development radical radiotherapy became more successful with the result of cure and longer survival time. Cure from the first malignancy and long survival are the preconditions for the development of a radiogenic secondary malignant neoplasm. Due to their longer life expectancy and their still growing organs children are particularly at risk [8, 15, 25, 27, 31, 33, 36, 38, 40, 42, 45, 46, 57, 59]. As one of the most serious late sequelae of radiotherapy, secondary malignancies can develop after a long latent period [4, 10, 20]. Most literature is about secondary malignant neoplasms in Hodgkin's disease and brain tumors.

Nasopharynx carcinoma (NPC) in children is rare [6, 35, 58] and often develops as a painless cervical swelling of enlarged, sometimes huge cervical lymph nodes. Epstein-Barr virus (EBV) infection is a known risk factor [41]. The 5-year overall survival rates are about 58% [3]. The prognosis in children is independent of gender and race [35, 43]. Distant metastases can develop in up to 40% of patients [2, 19, 43, 44, 48]. The current standard treatment of NPC in children is simultaneous radiochemotherapy [5, 14, 24, 53, 61].

We would like to report on a secondary malignancy 15 years after radical exclusive radiotherapy in a 12-year-old boy, who suffered from an advanced NPC. Written informed consent was obtained from the patient.

Case Report

Nasopharynx Carcinoma (NPC)

In 1983, a 12-year-old boy in good health and with an unremarkable personal history was sent to radiotherapy for a locoregionally advanced undifferentiated NPC, then called type Schmincke-Regaud. He presented with bilateral huge cervical lymph nodes. The CT demonstrated the primary tumor in the nasopharynx which reached far into the nasal cavity and into the oropharynx. Infiltration of the base of skull was confirmed by bone scintigraphy. The TNM category was cT3cN2M0 (UICC 1998).

Methods of radiotherapy for NPC. The portals were documented by simulation. Cobalt-60 (^{60}Co) photons were used for treatment. Lateral opposed fields included the base of skull and the regional levels II, III, and V. For level IV anteroposterior-posteroanterior (AP-PA) portals were used (Figure 1). For the phase after 39.6 Gy the portals for the primary tumor and cervical lymph nodes were split in order to spare the spinal cord. The fields were reduced posteriorly and supplemented by 9-MeV electron fields. In the supraclavicular regions midline blocks were used after 39.6 Gy for spinal cord sparing. A total dose of 59.4 Gy on the 90% isodose was given for the primary tumor and the cervical lymph nodes, single dose was 1.8 Gy. The supraclavicular region was irradiated to a total dose of 59.4 Gy on the ipsilateral left side and 50.4 Gy on the contralateral right side. The outer auditory canal was always included in the volume for the primary tumor and received a dose of 66.6 Gy. No concomitant chemotherapy was given. A skin reaction grade 2 and a mucositis grade 3 developed.

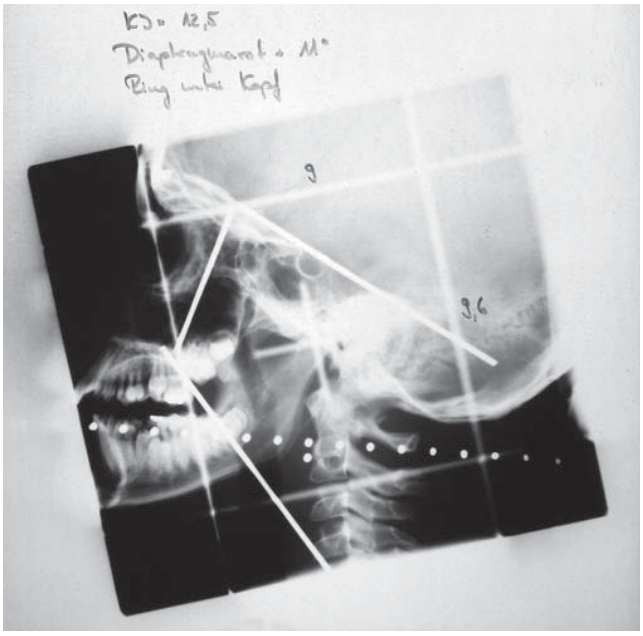

Figure 1. Lateral opposed simulator films of the first radiotherapy for nasopharynx carcinoma show the inclusion of the external auditory canal in the high-dose irradiation volume.

Abbildung 1. Seitlich opponierende Simulatoraufnahme der ersten Radiotherapie des Nasopharynxkarzinoms zeigen den Einschluss des äußeren Gehörganges in das Hochdosisvolumen.

Late effects of first radiotherapy. The NPC had remained in complete remission to date. The oral mucosa became atrophic and the patient lost his teeth as a consequence of xerostomia but did not suffer from severe side effects at first [17, 22, 23]. However, beginning in the 5th year after radiotherapy the then 17-year-old boy became symptomatic from diverse severe and clinically evident late effects.

As the first symptom a left phrenicus paresis appeared. 1 year later a paresis of the right N. V with dyskinesias occurred, and again 1 year later a right partial conduction deafness was diagnosed. At that time a hypoplasia of the ossicular chain bones and a marked atherosclerosis in both carotid arteries were shown on the CT scan. In the 8th year of follow-up an arterial hypertension was found. Meanwhile, the cervical spine had become heavily deformed (Figure 2), the right mandible hypotrophic and all cervical soft tissues atrophic.

In the 10th year after radiotherapy the meanwhile 22-year-old patient suffered from a thrombosis of the left jugular vein and the left brachiocephalic vein, and a collateral circulation in the upper thoracic aperture had developed (Figure 2). In both carotid arteries marked atherosclerosis was found [9, 50], and the patient was anticoagulated for the next 5 years.

The radiotherapy had also caused endocrinological alterations, which were clinically not significant and were diagnosed only at the time when preparation for postoperative radiotherapy of the secondary malignant neoplasm was organized. Basal TSH (thyroid-stimulating hormone) was significantly increased to 12.7 mU/l (normal range, 0.35–4.5 mU/l) with an FT_3 (free triiodothyronine) of 4.84 pmol/l (normal range, 3.5–6.5 pmol/l) and an FT_4 (free thyroxine) of 10.7 pmol/l, (normal range, 9.5–25 pmol/l). The TRH (thyrotropin-releasing hormone) profile showed a normal TSH response but an insufficient increase during the night. On sonography a small, hypotrophic thyroid gland with regressive alterations in both lobules was found, a further late side effect of radiotherapy. Those findings are indicative of a primary hypothyreosis and a small component of a secondary hypothyreosis caused by irradiation of the pituitary gland. A substitution with levothyroxine was initiated. The sex hormones showed the following baseline values: LH (luteinizing hormone) 10.8 U/l (normal range, 3–16 U/l), FSH (follicle-stimulating hormone) 24.9 U/l (normal range, 2–9 U/l), and testosterone 94.8 pmol/l (normal range, 66–142 pmol/l). Decreased stimulation indicated a dysfunction of Leydig cells. Caryotyping ruled out a Klinefelter syndrom, whereas alcohol abuse was considered the probable cause. The ACTH-cortisol axis and the growth hormone production were not involved.

13 years after treatment, a chronic eczema of the right external auditory canal was diagnosed for the first time, presumably the first hint at the later diagnosed secondary malignant neoplasm.

Microcystic Adnexal Carcinoma (MAC)

Diagnosis. In December 1998, 15 years after radiotherapy of the NPC, the meanwhile 28-year-old patient contacted his family practitioner because of increased pain in the right ear and progressive hearing loss. On clinical examination the right pinna was painful to touch and scaling crusts were found in the external auditory canal. A CT scan of the base of skull demonstrated a soft-tissue mass in the right external acoustic meatus extending to the right pyramid, and on the MRI scan a circular, contrast-enhancing infiltrating mass around the auditory canal was seen; suspect lymph nodes were not found. The first biopsy was diagnosed as a moderately differentiated squamous cell carcinoma.

Surgery. An extended lateral parotidectomy and a modified radical neck dissection of the levels II–IV were performed. The defect was closed with a flap of the pectoralis major muscle. The external auditory canal was reconstructed with a silicone catheter and a Thiersch graft. On the postoperative CT no macroscopic tumor rest was seen. The definitive histopathologic diagnosis described a typical MAC. The tumor showed a dissociated and infiltrating growth especially of the perineural sheaths, a focal squamous differentiation, and pseudoepitheliomatous hyperplasia (Figure 3). 18 lymph nodes were free of metastases, but the carcinoma reached the resection margins (R1 resection). Concerning the former radiotherapy, significant alterations were seen in the dermis and the underlying layers. Because of the incomplete resection and the histological aggressiveness we decided for a second radical radiotherapy.

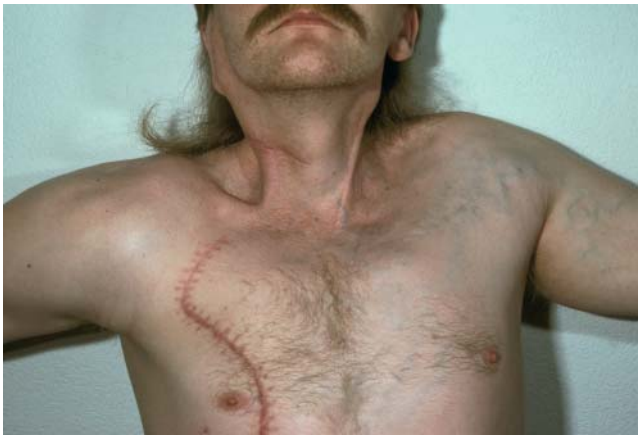

Figure 2. Musculoskeletal changes (atrophy of erector trunci muscles, kyphoscoliosis of the cervical spine), marked telangectasias in the previously irradiated regions, and extensive collateral circulation in the left thoracic aperture.

Abbildung 2. Muskuloskelettale Veränderungen (Atrophie des Erector trunci, Kyphoskoliose der HWS), deutliche Teleangiektasien der bestrahlten Regionen und ausgedehnter Kollateralkreislauf der linken Thoraxapertur.

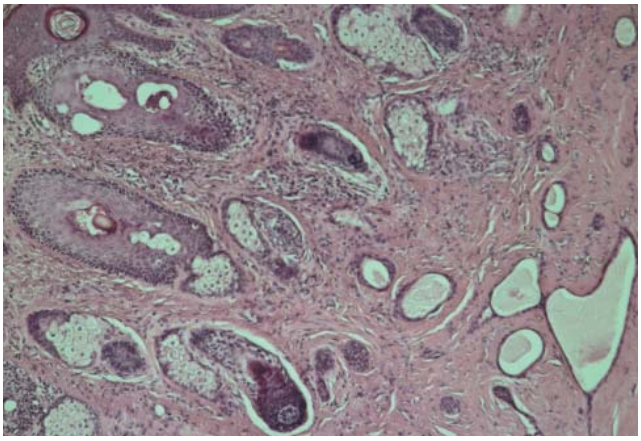

Figure 3. Histological specimen showing a typical microcystic adnexal skin carcinoma with extended dissociated and infiltrating growth, infiltration of perineural sheaths, focal squamous differentiation, and pseudoepitheliomatous hyperplasia, HE 25×.

Abbildung 3. Histologisches Präparat eines typischen mikrozystisch adnexalen Hautkarzinoms mit ausgedehntem dissoziierten und infiltrierenden Wachstum, Infiltration von Perineuralscheiden, fokal squamöser Differenzierung und pseudoepitheliomatöser Hyperplasie, HE 25×.

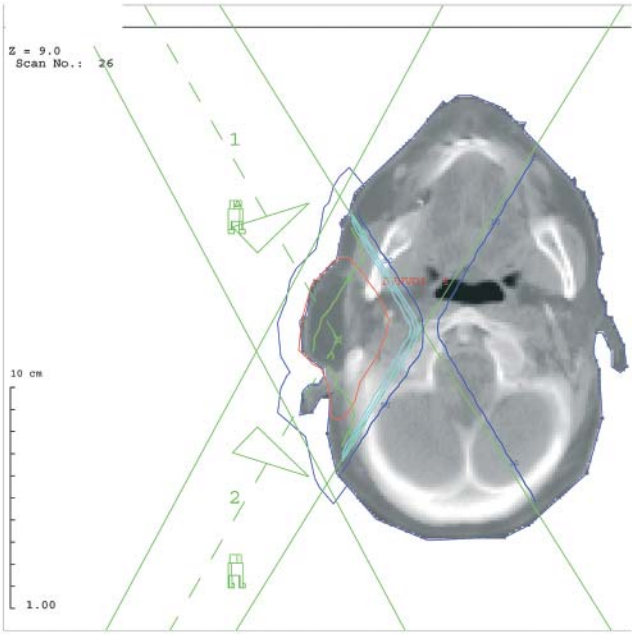

Figure 4. 3-D-planned dose distribution of convergent fields with delineation of planning target volume.

Abbildung 4. 3-D geplante Dosisverteilung mittels konvergierender Felder und Darstellung des PTV.

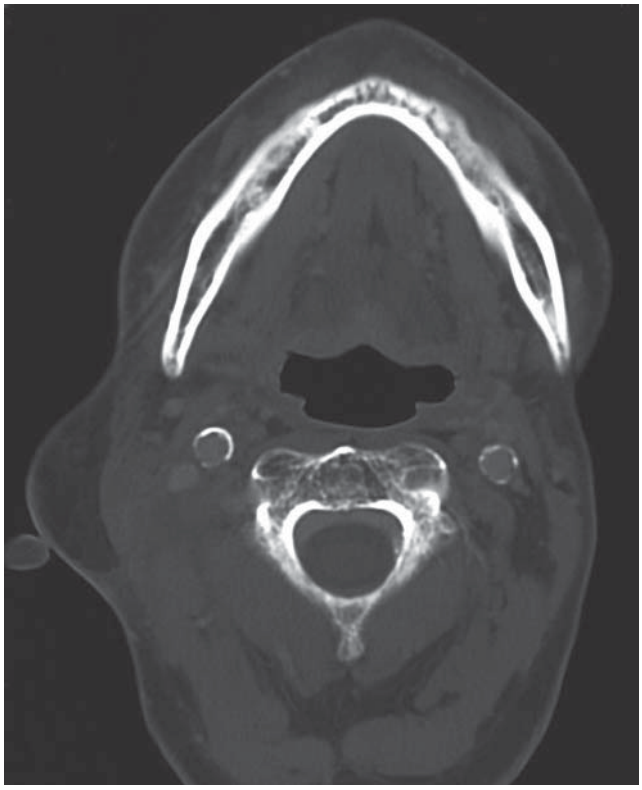

Figure 5. CT scan showing complete remission of the tumor with post-radiotherapeutic alterations in the flap tissue and marked atherosclerotic lesions in the carotid arteries.

Abbildung 5. CT mit kompletter Remission des Tumors, post-radiogenen Veränderungen im Lappengewebe und deutlicher Atherosklerose in den Karotiden.

Radiotherapy for MAC. At referral for the second radiotherapy, the patient had a Karnofsky index of 90. His height was 163 cm (normal height in comparison with his siblings) and his weight 60 kg. Blood pressure under medication was 120/80 mmHg. The flap in the right parotid region was healed, the patient had no immediate postoperative symptoms. Saliva production was reduced (unstimulated saliva flow 0.24 ml/min; stimulated 0.44 ml/min) and, as a consequence, the patient was edentulous.

As our standard treatment for a second course of radical irradiation after a first full-course radiotherapy, we employed a 3-D-based bifractionated (1 Gy b.i.d.) regimen and applied a total dose of 66 Gy in the ICRU point. The clinical target volume (CTV) encompassed the former tumor region of the resected auditory canal and the first lymphatic drainage to the parotid and the level II area. An isocentric application technique at the linear accelerator was used with convergent fields of 6-MV photons (Figure 4).

Radiotherapy was not combined with simultaneous chemotherapy which does not seem effective for MAC.

The second radiation treatment was surprisingly well tolerated; acute skin and mucosal reactions did never exceed grade 2 and disappeared within 6 weeks.

The patient was last seen 66 months after the second radiotherapy. He was in a good performance status. The tumor remained in complete clinical and radiologic remission. The patient reported occasional slight pain when opening his mouth which was already reduced after the first treatment, and discharge from the surgical scar. The last follow-up CT scan showed a complete remission, a fibrosis of the temporomandibular joint, and a streaky imbuement of the fatty tissues of the flap (Figure 5).

The most recent laboratory parameters included a macrocystic anemia (hemoglobin 105 g/l) probably as a consequence of chronic alcohol abuse. The substitution with levothyroxine was successful with a suppression of the basal TSH level to 0.003 and an increase in FT_3 and FT_4 to 6 and 24.2 pmol/l, respectively.

Discussion

We report on a rare case of MAC in the auditory canal that developed 15 years after radical radiotherapy for an NPC in a then 12-year-old boy, who was a second time successfully treated by subradical surgery and postoperative irradiation.

Since NPC in children is a rare disease, few data on secondary tumors after radiotherapy of NPC in children are found.

MAC was first defined in 1982 by Goldstein et al. [21]. In the literature mostly case reports are described [7, 30, 39, 47,

49], but never as a secondary malignant neoplasm after radiotherapy for NPC.

In a larger series of 27 patients, Antley et al. [1] showed most tumors to be second carcinomas after a radical radiotherapy. The carcinomas developed up to 30–40 years after irradiation. Preferred localizations were centrofacial and cervical regions; involvement of the ear is only reported twice [11, 28].

At clinical examination most often asymptomatic slowly growing nodules or cyst-like tumors are found, some presenting with a scar-like appearance [7, 10]. The tumor can be mistaken for other neoplasms, such as squamous cell carcinoma [7, 12, 13, 21] as in the first biopsy of our patient. There is a relationship of MAC with salivary and sweat gland tumors [60], since they share common histological features and chromosomal aberrations.

The MACs are locally invasive, destructive, and often infiltrate perineural sheaths [7]. It is difficult to obtain clean margins, as these tumors can spread far beyond the visible lesion [12]. They have a high recurrence rate; hematogenous metastases are rare [7, 20]. Surgery is recommended as the treatment of choice [12, 18], particularly Moh's microsurgery.

A gross tumor mass of MAC is commonly considered to be radioresistant [49]. A sequential treatment strategy of resection and radiotherapy is rational. For microscopic residual tumor the indication for radiotherapy is clearly given. This approach was validated in our case, in which the concept of a second radical radiotherapy 15 years after the first radical treatment was chosen instead of a further mutilating surgery followed by adjuvant radiotherapy [16, 26, 29, 32, 34, 37, 51–56]. The risk paid off, the patient is now 6 years in a complete remission and has no additional serious side effects after the second radiation treatment regimen.

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