Virchows Arch (1998) 433:391–394

CASE REPORT

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Double malignant neoplasms occurring long after local radiation to the oral mucosa

Received: 15 July 1997 / Accepted: 12 May 1998

Abstract A 59-year-old woman who had received cobalt-60 (^{60}Co) interstitial radiation therapy (total 44 Gy) in the right bucco-gingival region for inflammatory pseudotumour was found to have metachronous double malignant neoplasms. Initial osteosarcoma of the right mandibular angle and subsequent squamous cell carcinoma of the right buccal mucosa were identified 28 and 33 years after the radiation, respectively. Since both tumours were located very close to the focus of previous radiation, the therapy was considered to be responsible for their genesis. The patient had systemic metastases of the osteosarcoma.

Key words Inflammatory pseudotumour · Oral mucosa · Radiation · Osteosarcoma · Squamous cell carcinoma

Introduction

Since Billroth [3] first described multiple primary malignant neoplasms (MPMN) in 1889, several authors have proposed different definitions for this condition. The most widely used of these is that of Warren and Gates [23], who compiled 1259 cases of MPMN in 1932. Their diagnostic criteria were as follows: both tumours must be anatomically and histologically distinct, both must show clear signs of malignancy, and the possibility of one's being a metastasis of the other must be excluded. Although many cases have been reported as MPMN since then, almost all cases present a combination of epithelial malignancies; the co-occurrence of epithelial and non-epithelial malignancies appears to be rare. The simultaneous occurrence of two histologically distinct primary malignancies in the same organ is also extremely rare [14]. Here we describe a case with double malignant neoplasms: an osteosarcoma arising in the right mandibular angle and a subsequent squamous cell carcinoma arising in the right buccal mucosa. This combination is the first description of double malignant neoplasms associated with and possibly caused by previous radiation therapy. We estimate and discuss the effects of radiation on the loci at which the two neoplasms developed with radiation diminishing theories.

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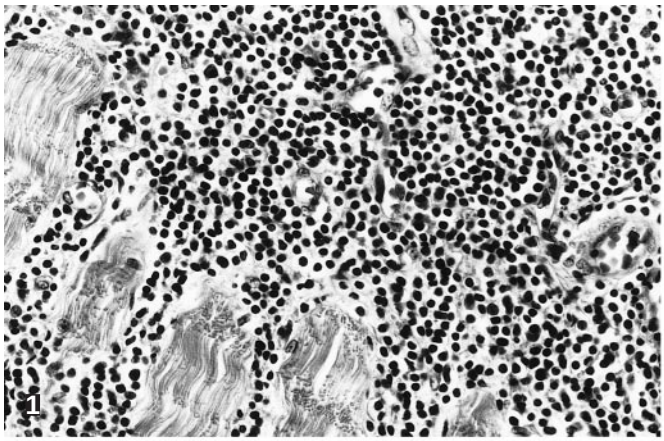
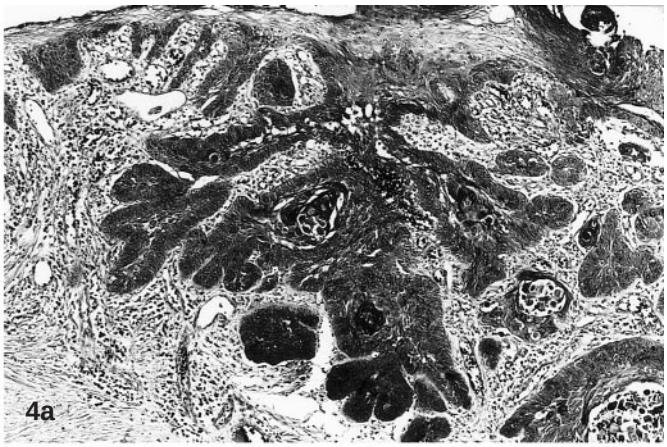
Case history

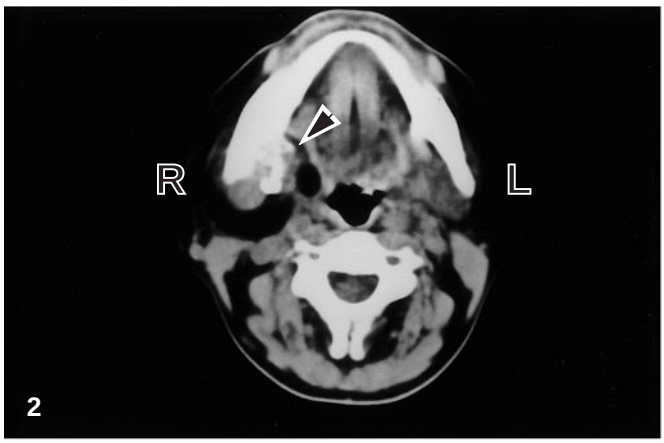
A 21-year-old woman visited a dental clinic in February 1956, with the chief complaint of swelling and an ulcer formation in her right buccal mucosa after treatment for marginal periodontitis of the right maxillary third molar tooth. Although the right maxillary second and third molar teeth were extracted, the symptoms were not relieved. In August 1956 she was referred to the Tohoku University Medical Hospital. The first intraoral examination revealed extreme swelling from the right alveolar tubercle to the buccal mucosa without ulcer formation. Clinicians suspected a tumour in the right maxilla, and the mass was excised. The surgically removed material was approximately 13×6 cm in size and 140 g in weight. Histological examination showed a granulomatous lesion made up of marked inflammatory cells and cellular fibrosis without atypia, and the lesion was diagnosed as inflammatory pseudotumour (IP). Subsequently, the patient was treated with ^{60}Co interstitial radiation with 5 needles 3 cm in length (2 mCi, single-plane implants, approximately 3×3 cm in area) for 5 days (total 44 Gy) at the site, after complete removal of the tumour. During the interstitial radiation therapy, one of the needles was unfortunately exposed at the surface of the mucosa near the radiation area for at least 1 day, after which it was re-inserted into the original position.

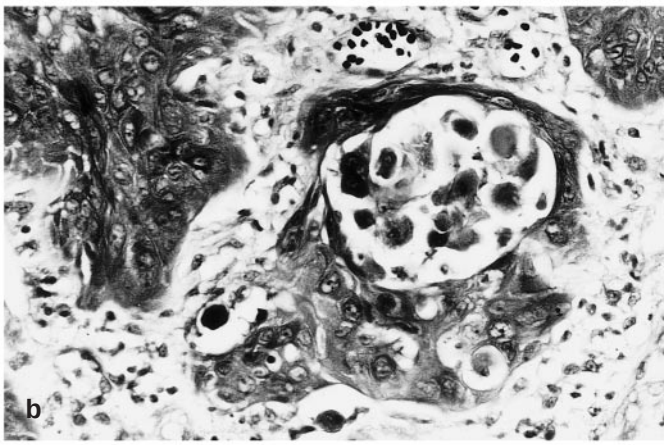
In August 1977, 21 years after the initial episode, the patient was admitted to the Oral Surgery Department of Tohoku University Dental Hospital with a complaint of a painless mass around the coronoid process of the mandible to the right temporal muscle. It was located approximately 2 cm from the centre of the previous radiation site. The mass was excised, and no follow up radiation therapy was administered. Histological examination of the mass showed the infiltration of numerous inflammatory cells, predominantly lymphocytes, in the degenerating muscle tissue (Fig. 1). The pathological diagnosis was again IP; the tumour was considered to be the basically the same tumour as the previous one, and no evidence of sarcoma was identified.

In October 1984, 28 years after radiation therapy, the patient became aware of a nodular mass in the right mandibular angle, the site of which was approximately 3 cm away from perpendicular to









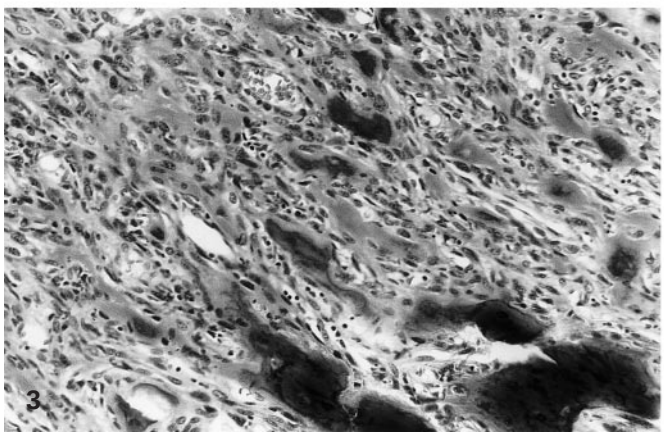


Fig. 1 Photomicrograph of the inflammatory pseudotumour. The tumour consists of infiltrated severely inflammatory cells, predominantly lymphocytes, and degenerative muscle fibres. Haematoxylin-eosin, original magnification ×80

Fig. 2 An axial view of the computed tomography scan demonstrates a destructive lesion (*arrowhead*) in the right mandibular angle and a soft tissue mass

Fig. 3 Photomicrograph of the osteosarcoma. The tumour cells are proliferating with numerous osteoid formation. Haematoxylin-eosin, original magnification ×20

Fig. 4 **a** Photomicrograph of squamous cell carcinoma. Invasive proliferation of well-differentiated squamous cell carcinoma into the submucosa is seen. Haematoxylin-eosin, original magnification ×5. **b** High-power view. Individual squamous cell carcinoma cells with moderate stromal reaction. Haematoxylin-eosin, original magnification ×100

the square area where the radiation needles had previously been inserted. The tumour rapidly increased in size, and a computed tomography scan demonstrated cortical destruction of the right mandibular angle and an associated soft tissue mass (Fig. 2). Unfortunately, systemic bone scintiphotography was not performed at this time, but the patient had no bone pain in any other sites and had not shown any other bony abnormalities on physical examination except for the mandibular bone lesion. The biopsy specimen showed the proliferation of spindle-shaped or pleomorphic neoplastic cells. They had abundant mitotic figures and often multinucleated giant cells with partial but apparent osteoid formation (Fig. 3). The pathological diagnosis was osteosarcoma arising in the mandible, and partial right mandibular resection and radical neck dissection were performed for total removal. The surgical margins of the resected specimen were free from tumour cells.

An erosive lesion in the right buccal mucosa was noticed within the area of the previous radiation in October 1989, 33 years after the radiation therapy. Histological examination showed invasive proliferation of well-differentiated squamous cell carcinoma into the submucosa (Fig. 4a, b), which showed prominent cancerous pearls with stromal desmoplastic reaction. The whole tumour was surgically resected, and no recurrence of the carcinoma was present after the surgery.

Subsequently there was a osteosarcoma relapse in the right cervical lymph node in October 1989, and metastatic nodules gradually increased in systemic organs. The patient died on March 3, 1994, the immediate cause of death being respiratory failure caused by multiple and massive metastases of the osteosarcoma to both lungs. Autopsy revealed an exophytic extension with necrosis of the osteosarcoma 15×10×6 cm in size at the local site of the op-

eration on the right mandible and a right sublingual nodular mass 5 cm in diameter, with continuous invasion to the left side of mandibular bone. Metastases of the osteosarcoma were present in the subcutis of the scalp (several, up to 4 cm in diameter), the thyroid gland (single, 1 cm in diameter), both lungs (multiple, up to 12 cm in diameter), the liver (several, up to 1 cm in diameter), both adrenal glands (several, up to 1 cm in diameter), both kidneys (several, up to 2 cm in diameter), the pancreas (involving the whole pancreas), the parietal bone (several, up to 2 cm in diameter), the costal bones (left 5th and right 6th), the ilium (left iliac wing) and the systemic lymph nodes (peritracheal, periesophageal, peripancreatic, paraaortic, both pulmonary hilar and peritoneal regions). Neither local recurrence of nor distant metastasis from squamous cell carcinoma was present.

Discussion

IP is an uncommon nonneoplastic lesion of unknown cause, which occurs most commonly in the lungs and liver [8]. IP in the oral and maxillofacial region is rare, but several IP cases have been reported, in the maxillary sinus [11, 21], cheek [10], and mandible [25]. Whereas surgical excision is one of the treatments, radiation therapy is still thought to be effective in patients with recurrent or inoperable cases [8, 19]. Although potential side effects of radiation should be taken into consideration, especially with young patients, the choice of radiation therapy in the present case was considered to be reasonable after removal of the tumour because of the huge mass of the IP (13×6 cm).

However, the possibility exists that in the present case the “IP” could have been a very early stage of myositis ossificans, since several cases of osteosarcoma arising in myositis ossificans have been reported [1, 9].

Interstitial radiation therapy is now regarded as an excellent modality for carcinoma of the oral region (especially the tongue), the organs of the urinary system, the genital organs and the breast, as a means of delivering a high dose of radiation to malignant tumours while sparing the surrounding normal tissue [7]. Radiation therapy can provide a cure rate higher than or comparable to that obtained with surgery, especially in smaller tumours, and also offers a greater potential for preservation of the shape and function of the oral cavity [18]. However, radiation-related complications sometimes occur in soft tissue or bones. One of the most severe complications after radiation therapy for tongue cancer is osteoradionecrosis of the mandible [6]. In addition, in the long term, there is the possibility of radiation-induced malignant neoplasms. When there is a sufficient distance between the radioactive focus and the normal tissue, the radiation dose to the normal tissue is markedly reduced: to less than 3% of that to the malignant site within a distance of approximately 3 cm from the source according to data reviewed by Quimby [17]. According to this theory, in the present case it is estimated that the normal site corresponding to mandibular osteosarcoma might have received a dose of approximately 1.5 Gy, which would have the ability to induce secondary neoplasms [22]. Since the site of buccal squamous cell carcinoma was entirely within the previous radiation area, it is evident that the site had been exposed to almost the same dose as was measured at the radiation source. Additionally, the ^{60}Co needle exposure on the mucosa might have played an unpredictable part in increasing the effect on surrounding tissue, especially the mandible.

In general, determination of the effects of interstitial radiation is complicated by several factors, such as the variation in metabolism of the different isotopes, their energy spectra, biological half-lives and the distribution and concentration in particular tissues. However, the interstitial radiation administered to this patient was considered to be effective at both loci even though the doses were estimated as low in one neoplasm site. Furthermore, the latency periods in the present case (28 and 33 years, respectively) are sufficiently long intervals for tumourigenesis compared with the “median latency period (13 years)” recently reported from the Mayo Clinic [5].

The incidence of double neoplasms occuring in one individual whether synchronously or metachronously is said to be approximately 1–3 % for all kinds of neoplasms [15]. According to a study by Nakamura et al. [15], in which 52 cases with double malignant neoplasms associated with the maxillo-facial region were examined from 1951 to 1978 in Japan, the most frequently seen combination of tumours developed in the oral cavity mucosa and the alimentary tract (28 cases, 53.8%), especially the stomach (18 cases, 34.6%). This result may be associated with the fact that gastrointestinal carcinoma is one of the most common neoplasms in Japan.

Moertel et al. [13] classified patients with MPMN topographically into those with MPMN of the same tissue or organ, with multicentric lesions of the same organ or the same tissue in contiguous organs or in bilaterally paired organs and those with MPMN of different organs. They also used a chronologically classification into synchronous (2 or more cancers present at the same time or within 6 months of the first primary cancers) and metachronous (first malignant neoplasm is followed by a second one at a later date). Our case was one of tumours at one site at different times.

Recently, it has been emphasized that the pathogenesis of MPMN may be closely associated with genetic background, and especially with the germline mutation of p53 in Li-Fraumeni syndrome [24]. However, one of the criteria of the syndrome (age under 40 years) does not fit the present case, and the patient had a definite history of radiation that had the potential to cause malignant neoplasms [16].

Three cases of bone sarcoma related to the external radiation were described in 1922 by Beck [2], who noted the appearance of pleomorphic spindle cell sarcomas in patients who had undergone radiation for tuberculous arthritis. Osteosarcoma secondary to inadvertent ingestion of radium-226 was reported soon after by Martland and Humphries [12]. They pointed out the appearance of osteosarcoma in watch dial painters who were in the habit of putting their brushes in their mouths to get the bristles to a point.

In 1948, Cahan et al. [4] proposed criteria for the diagnosis of postradiation sarcoma: there must be microscopic or radiographic evidence of a benign initial lesion or a malignant lesion devoid of osteoblastic activity; sarcoma must have developed within the radiated field; there must be a relatively long period of latency (more than 3 years); and the sarcoma must be confirmed histologically. The initial lesion in the present case was IP, and the mandibular bone was clinically normal at that time. Hence, we believe that the present case fulfils these criteria.

Relatively few studies have been performed of squamous cell carcinomas arising in mucosa associated with radiation therapy, especially in the oral mucosa [20]. One reason may be that it is difficult to evaluate whether the neoplasms are a coincidence or a local recurrence. In the present case, however, radiation therapy was performed to tread an IP which was apparently a different kind of tumour from the subsequent neoplasms.

The present case showed an episode of radiation with a sufficiently long interval for the formation of both tumours, had a rare coexistence of inflammatory pseudotumour, mandibular osteosarcoma and buccal stratified squamous cell carcinoma in one individual, and showed close localization of the two lesions and no evidence of genetic predisposition, although historical techniques were the only ones used in investigation. We were able to follow up the present case for quite a long time in our institute, with a complete patient history record, which was especially helpful in detailed evaluations of the relationship between the radiation therapy and the later tumours.

References

1. Auerbach O, Friedman M, Weiss L, Amory HI (1951) Extraskeletal osteogenic sarcoma arising in irradiated tissue. Cancer 4:1095–1106
2. Beck A (1922) Zur Frage des Röntgensarkoms, zugleich ein Beitrag zur Pathogenese des Sarkoms. Munchen Med Wochenschr 69:623–625
3. Billroth T (1889) Die allgemeine chirurgische Pathologie und Therapie in 51 Vorlesungen, ein Handbuch fur Studierende und Ärzte. In: Billroth T (ed) Ein Handbuch fur Studierende und Ärzte. Reimer, Berlin
4. Cahan WG, Woodard HQ, Higinbotham NL, Stewart FW, Coley BL (1948) Sarcoma arising in irradiated bone. Cancer 1:3–29
5. Frassica FJ, Frassica DA, Wold LE, Beabout JW, Sim FH (1993) Postradiation sarcoma of bone. Orthopedics 16: 105–106
6. Fujita M, Hirokawa Y, Kashiwado K, et al (1996) An analysis of mandibular bone complications in radiotherapy for T1 and T2 carcinoma of the oral tongue. Int J Radiat Oncol Biol Phys 34:333–339
7. Horiuchi J, Okuyama T, Shibuya H, Takeda M (1982) Results of brachytherapy for cancer of the tongue with special emphasis on local prognosis. Int J Radiat Oncol Biol Phys 8:829–835
8. Imperato JP, Folkman J, Sagerman RH, Cassady JR (1986) Treatment of plasma cell granuloma of the lung with radiation therapy. A report of two cases and a review of the literature. Cancer 57:2127–2129
9. Järvi OH, Kvist HTA, Vainio PV (1968) Extraskeletal retroperitoneal osteosarcoma probably arising from myositis ossificans. Acta Pathol Microbiol Scand 74:11–25
10. Liston SL, Dehner LP, Jarvis CW, Pitzele C, Huseby TL (1981) Inflammatory pseudotumors in the buccal tissues of children. Oral Surg Oral Med Oral Pathol 51:287–291
11. Maldjian JA, Norton KI, Groisman GM, Som PM (1994) Inflammatory pseudotumor of the maxillary sinus in a 15-year-old boy. AJNR Am J Neuroradiol 15:784–786
12. Martland HS, Humphries RE (1929) Osteogenic sarcoma in dial painters using luminous paint. Arch Pathol 7:406–417
13. Moertel CG (1977) Multiple primary malignant neoplasms. Historical perspectives. Cancer 40:1786–1792
14. Nakahara H, Kitamura R, Shirasuna K (1995) Simultaneous malignant melanoma and squamous cell carcinoma of the oral cavity: a case report. J Oral Maxillofac Surg 53:1455–1457
15. Nakamura H, Matuura M, Inamura T, Seto K (1979) Double cancers of the oral region: a case report and a survey of subject literature. Tsurumi Univ Dent J 5:11–17
16. Prasad KN (1974) Radiation carcinogenesis. In: Prasad KN (ed) Human radiation biology. Harper & Row, Hagerstown, pp 341–356
17. Quimby EH (1944) Dosage table for linear radium sources. Radiology 43:572–577
18. Schmidt-Ullrich R, Zwicker RD, Wu A, Kelly K (1991) Interstitial IR-192 implants of the oral cavity: the planning and construction of volume implants. Int J Radiat Oncol Biol Phys 20:1079–1085
19. Seider MJ, Cleary KR, van Tassel P, et al (1991) Plasma cell granuloma of the nasal cavity treated by radiation therapy. Cancer 67:929–932
20. Slaughter DP, Southwick HW (1957) Mucosal carcinomas as a result of irradiation. Arch Surg 74:420–429
21. Som PM, Brandwein MS, Maldjian C, Reino AJ, Lawson W (1994) Inflammatory pseudotumor of the maxillary sinus: CT and MR findings in six cases. AJR Am J Roentgenol 163: 689–692
22. Suvarna SK, Bagary M, Glazer G (1993) Radiation-induced squamous carcinoma arising within a seborrhoeic keratosis. Br J Dermatol 128:443–447
23. Warren S, Gates O (1932) Multiple primary malignant tumors. A survey of the literature and a statistical study. Am J Cancer 16:1358–1414
24. Williams KJ, Boyle JM, Birch JM, Norton JD, Scott D (1997) Cell cycle arrest defect in Li-Fraumeni syndrome: a mechanism of cancer predisposition? Oncogene 14:277–282
25. Zegarelli DJ, Rankow RM, Zegarelli EV (1974) A large dental granuloma (? inflammatory pseudotumor) with unusual features: report of case. J Am Dent Assoc 89:891–894