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內文：

Abstract

- Radiation-induced sarcoma (RIS) or postirradiation sarcoma has been reported rarely as a long-term complication of radiation therapy (RT).
- Histopathological evaluation and immunohistochemical study were performed using a panel of markers including vimentin, cytokeratin, S-100, desmin, myoglobin, HHF-35, p53, and p16
 - ✓ Vimentin -- 4(+)
 - ✓ Cytokeratin -- 4(-)
 - ✓ myoglobin, desmin, HHF-35 -- 2(+) → myogenic origin
(One case → fibrosarcoma ; the other → not specified)
 - ✓ Diverse expression of p53 and p16
- Report of the complicated clinical processes and the analysis of genetic markers of these cases provide useful clinical and pathogenetic insights of mesenchymal malignancies associated with a status post OSCC radiation

Introduction

- High dosage of postoperative radiation therapy(RT)
 - advanced (stages III and IV) oral squamous cell carcinoma(OSCC)
 - carcinogen
- Very rare cases of radiation-induced sarcoma (RIS) after OSCC were reported
- In 2000, Mertens et al. first described the chromosome aberrations in cases of RIS
- Tarkkanen et al. further analyzed the difference of genetic changes between sporadic sarcoma and RIS by using comparative genomic hybridization
- Tumor suppressor gene (TSG)
 - ✓ p53 → induction of apoptosis in cells suffering from irreversible genetic defects as a result of ionizing radiation.
 - mutation is associated with a poor response to radiation therapy
 - ✓ P16 → inactivation or down-regulation of p16 (CDKN2a/INK4a) is required to immortalize the cells
 - abnormal function of p16 is associated with local treatment failure in radiotherapy.
- the lack of normal functioning of TSGs, such as p53, p16, and others, have been correlated significantly with the transformation or progression of many malignancies, especially those having received high efficient megavoltage radiation therapy

Case report

Table 1. Summary of 4 cases

Case	Age, y/Sex	Primary OSCC				Sarcoma		
		Diagnosis	Location	Radiation dose, Gy	Latency, mo	Origin	Treatment	Outcome
1	55/F	SCC, T3N0M0	Tongue	80 BRT 103 XRT	40	Muscular	Surgery, RT	DOD
2	63/M	SCC, T3N0M0	Palate	65 XRT	9	Fibroblastic	Surgery, CT	DOD
3	64/M	SCC, T4N0M0	Buccal mucosa	70 XRT	25	ND	Surgery, CT	DOD
4	66/M	SCC, T4N1M0	Buccal mucosa	66 XRT	50	Muscular	Surgery, CT	DOD

Case1

Age : 55y/o

Sex : Female

History : A(-) B(-) C(+)

1996

Lesion : 2-cm ulcerative lesion in the right ventral tongue and mouth floor

Pathological : squamous cell carcinoma (SCC)

→ therapeutic dose of 8000 cGy in 40 fractions for the primary lesion and an additional dose of 5587 cGy in the right neck and 4687 cGy in the left submandibular area

1999

Lesion : 2 x 2 cm bulging mass occurred in the mucosa of the right cheek

Pathological : granulation tissue

2000 July

Lesion : grew rapidly into a 4 x 3-cm mass within 1 month, protruding from the right buccal mucosa, extending to the right side of the tongue, mouth floor, and submandibular region without evidence of neck lymphadenopathy.

Pathological : rhabdomyosarcoma

→ radiotherapy for 6200 cGy and chemotherapy

Case2

Age : 57 y/o

Sex : male

History : A(+) B(+) C(+)

1994

Lesion : 2.5 x 2 cm indurated, ulcerative exophytic mass over the right side of the palate for 2 months

Pathological : SCC final staging of pT3N0M0, stage III

→ wide excision

2000 December

Lesion : 2 x 2 cm new mass was found over the right palate again

Pathological : well-differentiated SCC

→ was excised with a 1-cm safe margin

2001 June

Lesion : tumor recurred and extended to the underlying bone, right upper gingival, and soft palate.

→ Wide excision operation plus right side partial maxillectomy was performed

Radiation therapy with a total dosage of 6480 cGy

2002 March

Lesion : 3.5-cm exophytic mass with a smooth surface on the right buccal mucosa

2.5-cm exophytic and ulcerative mass over the median border of the palate adjacent to the surgical margin of previous partial maxillectomy

Pathological : a sarcoma in the buccal mucosa and a recurrent SCC in the palate

→ chemotherapy

Case3

Age : 62 y/o

Sex : male

2001 March

Lesion : gingival SCC of the right mandible

→ Radiation therapy with a total dosage of 7020 cGy

2002 March

Tumor recurred

Pathological : stage IV pT4N0M0 SCC

→ Wide excision with radical neck dissection

2003 March

Lesion : a 1 x 1-cm ulcerative lesion over the right lower gingiva adjacent to the previous surgical site

Pathological : recurrent SCC

After surgery

Lesion : a 3 x 3-cm bulging-out soft tissue mass occurred in the right submental area perforating through the skin

Pathological : sarcoma

→ another ablative excision with partial mandibulectomy

After surgery, only chemotherapy

Case 4

Age : 62 y/o

Sex : male

History : A(+) B(+) C(+)

1999 January

Lesion : 4 X 5-cm exophytic ulcerative, indurated mass over the left buccal mucosa.

a firm, but movable 2-cm neck mass with a central necrosis pattern in CT scan

Pathological : SCC(pT4N1M0, stage IV).

→Wide excision combined with radical neck dissection was performed

chemoradiotherapy was given with a total radiation dosage of 6600 cGy in 33 fractions

2003 April

Lesion : a 3 x 2-cm new hemorrhagic soft mass lesion was found over the right buccal mucosa

Pathological : sarcoma.

→ wide excision

2003 September

sarcoma recurred again in the previously dissected region with neck metastasis

→chemotherapy

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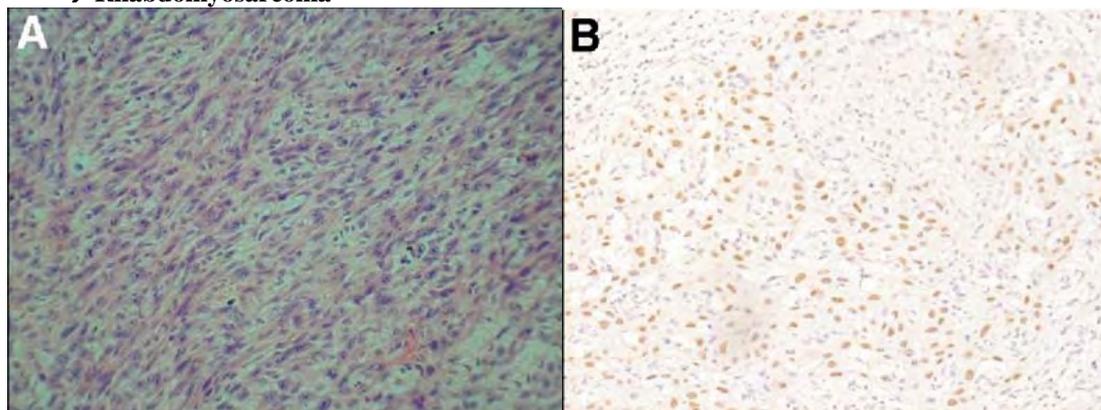
- Hematoxylin and eosin(H&E) stain
- The primary antibodies for IHC included those against cytokeratin, vimentin, S-100, desmin, myoglobin, HHF-35 and p53, and p16
- Cell content $\leq 10\%$ was considered positive (+) in cases with strong staining, while positive cell content less than 10% was considered negative (-). Case of ambiguous immunoreactivity was recorded as (+/-).

RESULTS

Histopathology of tumors after radiotherapy

Case 1

- Histological observation revealed spindle and pleomorphic malignant cells with eosinophilic cytoplasm.
 - IHC for cytokeratin (-), vimentin (+), myoglobin (+). HHF-35 (-)
- Rhabdomyosarcoma

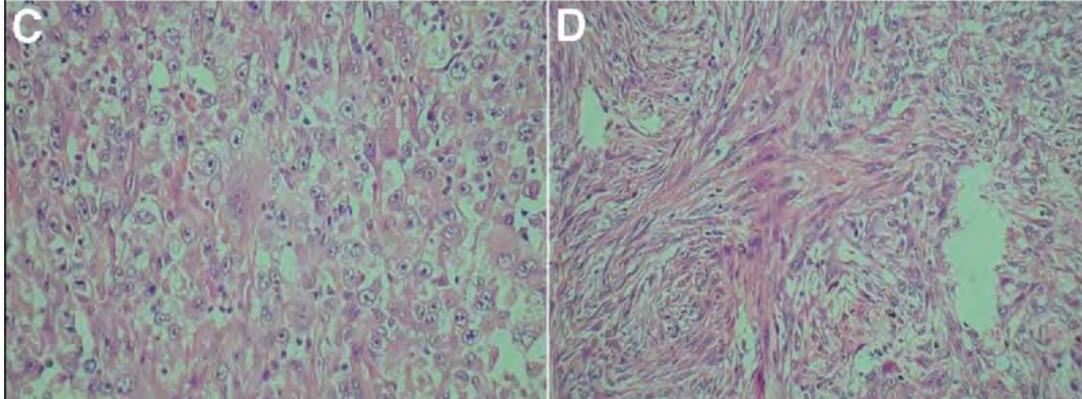


Case 2

- Histological evaluation of the buccal mucosa lesion revealed a diffuse infiltration of spindle-shaped tumor cells arranged in a fascicle pattern, with pale eosinophilic cytoplasm and plump cigar-shaped nuclei. Prominent nucleoli and frequent mitotic figures were present
 - Vimentin (+) , cytokeratin(-), HHF-35(-), desmin(-), myoglobin(-)
- fibrosarcoma
- in the other lesion localized to the palate, nests of well-differentiated SCC with stromal invasion were observed.
 - cytokeratin(+), vimentin(+), HHF-35(-), myoglobin(-), S-100(-)

Case 3.

- **Histological evaluation showed stromal tissue and skeletal muscle infiltrated with mainly plump polyhedral cell clusters and some short spindle-shaped tumor cells.**
- **These tumor cells appeared pale and plump with eosinophilic cytoplasm, prominent nucleoli, pleomorphism, and frequent mitotic figures**
- **vimentin (+), cytokeratin (-), HHF-35 (-), desmin (-), S-100 (-).**



Case 4.

- **Sections of the excised mass showed a picture of sarcoma composed of spindle cells in a fascicle, whorl, or occasional herringbone arrangement.**
- **Eosinophilic cytoplasm and plumped hyperchromatic nuclei with frequent mitoses were seen in tumor cells**
- **vimentin(+), desmin(+), HHF-35(+), CD117(-)
→ leiomyosarcoma**

Table II. Expression of tissue markers in sarcomas

Case	Sarcoma					
	Cytokeratin	Vimentin	S-100	Desmin	Myoglobin	HHF35
1	-	+	-	-	+	-
2	-	+	-	-	-	-
3	-	+	-	-	-	-
4	-	+	-	+/-	-	+/-

+/- represents heterogeneous weak positive.

Case 1 → rhabdomyosarcoma

Case 4 → leiomyosarcoma

Case 2 → fibrosarcoma.

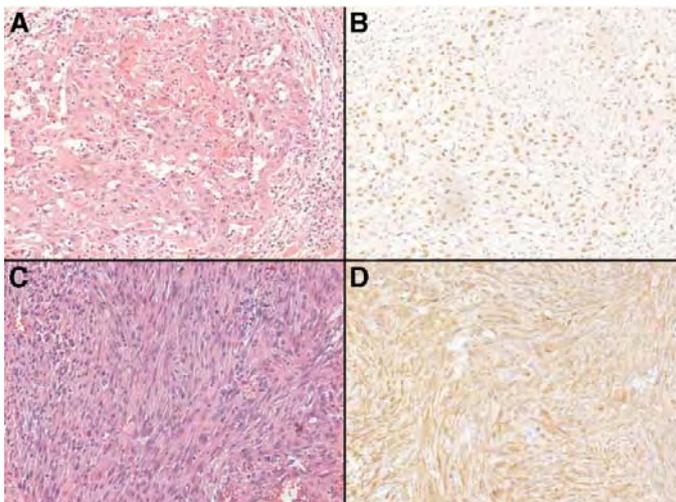
Case 3 → could not be defined with these markers

IHC for p53 and p16 of the primary OSCC and sarcoma

Table III. p53 and p16 immunoreactivity in primary OSCC and sarcoma

Case	OSCC		Sarcoma	
	p53	p16	p53	p16
1	NA	NA	+	-
2	+	-	+	+/-
3	-	-	-	-
4	+	-	-	+

+/- represents heterogeneous weak positive; NA, not available.



DISCUSSION

1. The occurrence of sarcomas in the head and neck region is rare.
 - only 4.2% of 3796 sarcoma patients (Patel et al.)
2. Etiology of sarcomas
 - ✓ tumorigenic effects of prior radiation therapy
 - ✓ the spontaneous development of second malignancies in the form of sarcomas
3. The criteria used for the diagnosis of RIS in irradiated bone as follows:
 - (1) history of radiation therapy
 - (2) the development of neoplasm within the field of the radiotherapeutic beam
 - (3) histological proof of a sarcoma
4. Incidence of radiation-induced secondary cancers (in the head and neck region) → 0.70%
 - Most of the radiation-induced malignancies → Carcinoma ; RIS
5. Histopathology → osteosarcoma, malignant fibrous histiocytomas, and fibrosarcoma
6. p53 → regulating cell cycle, genomic stability, differentiation, and apoptosis
 - Overexpression of mutant p53 → oral tumorigenesis
 - p16 → negative cell-cycle regulator
 - Enhances radiation-induced cell killing
 - p53 and p16 alterations have been recognized in association with the treatment response to radiation therapy and the consequent occurrence of radiation-induced malignancies
7. Successful treatment of RIS is difficult
 - ✓ difficulty in determining their surgical safe margins
 - ✓ regional metastasis of sarcomas in the head and neck after surgery occurred frequently

CONCLUSIONS

- To implicate radiation therapy in the causation of tumors is difficult.
- When tumors occur that are histologically or phenotypically different from the primary cancer and having radiation history, the possibility of radiation-induced malignancy should be taken into consideration.

題號	題目
1	免疫組織化學染色中,那一個 marker 不能當作鑑別 tumor 的來源是中胚層 (A) Cytokeratin (B) Desmin (C) Myoglobin (D) HHF35
答案(A)	出處： http://www.medicalab.com.tw/
題號	題目
2	以下何者已被證實跟抑制癌症有關的基因? 1. p16 2. p21 3. p53 4. p86 (A) 1,2,3 (B) 2,3,4 (C) 1,2,4 (D) 1,3,4
答案(A)	出處： http://www.medicalab.com.tw/