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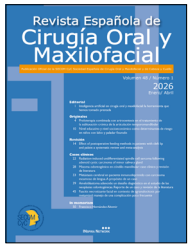

Clinical case

Radiation-induced undifferentiated spindle cell sarcoma following adenoid cystic carcinoma of minor salivary gland

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ABSTRACT

Radiotherapy is an established treatment for head and neck neoplasms. Despite its usefulness, it can rarely lead to radiation-induced malignancies. Radiation-induced spindle cell sarcoma is an uncommon entity, particularly after adenoid cystic carcinoma treatment.
We present a case of a 73-year-old woman who developed an undifferentiated spindle cell sarcoma six years after undergoing surgical resection and adjuvant radiotherapy for adenoid cystic carcinoma of a minor salivary gland in the floor of the mouth. The diagnosis was initially delayed due to prior osteoradionecrosis and osteomyelitis. The lesion was considered unresectable and treatment with systemic chemotherapy was initiated; however, the patient died four months later.
This case illustrates the diagnostic challenges in previously irradiated and surgically altered tissues. It emphasizes the importance of a high level of suspicion and the necessity of early biopsy when new or progressive lesions emerge in irradiated areas.

Sarcoma fusocelular indiferenciado radioinducido tras un carcinoma adenoide quístico de glándula salival menor

Palabras clave:

Neoplasias de cabeza y cuello, neoplasias de glándulas salivales, glándulas salivales menores, neoplasias inducidas por radiación, sarcoma.

RESUMEN

La radioterapia es un tratamiento ampliamente establecido para las neoplasias de cabeza y cuello. A pesar de su utilidad, en raras ocasiones puede dar lugar al desarrollo de neoplasias radioinducidas. El sarcoma fusocelular radioinducido es una entidad poco frecuente, especialmente tras el tratamiento de un carcinoma adenoide quístico.
Presentamos el caso de una mujer de 73 años que desarrolló un sarcoma fusocelular indiferenciado seis años después de la resección quirúrgica y radioterapia adyuvante de un

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carcinoma adenoide quístico de glándula salival menor del suelo de la boca. El diagnóstico se retrasó inicialmente debido a los antecedentes de osteorradionecrosis y osteomielitis. La lesión fue considerada irresecable y se inició tratamiento con quimioterapia sistémica; sin embargo, la paciente falleció cuatro meses después.

Este caso pone de manifiesto las dificultades diagnósticas en tejidos previamente irradiados y sometidos a cirugía, y destaca la importancia de mantener un alto índice de sospecha clínica y la realización de una biopsia precoz ante la aparición de lesiones nuevas o progresivas en áreas irradiadas.

INTRODUCTION

Adenoid cystic carcinoma (ACC) is a malignant tumor of the salivary glands, that represents approximately 1 % of all head and neck malignant neoplasms and about 10 % of salivary gland malignancies. It most commonly arises from minor salivary glands, particularly in the palate and other sites of the oral cavity.

ACC usually shows a slow-growing behavior at early stages; however, it is associated with a high risk of local recurrence and late distant metastasis, characteristically in lungs. The use of adjuvant radiotherapy following surgical treatment is often supported in advanced disease or when adverse pathological factors are identified[1,2].

Despite the usefulness of radiotherapy as treatment, it can rarely lead to radio-induced sarcomas (RIS) after a variable latency period. Though its incidence is low, the aggressive behavior and poor prognosis of this condition, coupled with the expectation of an increase in cases due to improved patient survival and increased indications for RT, makes early recognition clinically relevant.

The histological subtypes of RIS in head and neck area are heterogeneous. Osteosarcoma and fibrosarcoma are the most frequently reported, whereas soft tissue sarcomas such as spindle cell sarcoma are considerably less common.

RIS often present with nonspecific signs and symptoms that may mimic more common post-radiation complications, such as osteoradionecrosis, chronic infection, or inflammatory changes. This can lead to delayed diagnosis, particularly in the early stages, when intervention could be most beneficial.

The management of radiation-induced sarcomas remains challenging due to their rarity, histological diversity, and anatomical limitations resulting from prior irradiation of the affected tissues. Surgical resection with wide margins is generally considered the primary treatment option when feasible, although local control is often challenging to achieve[3-5].

The aim of this report is to describe a rare case of radiation-induced undifferentiated spindle cell sarcoma following radiotherapy for adenoid cystic carcinoma of a minor salivary gland, an association that has been only rarely reported in the head and neck area.

CASE REPORT

Initial diagnosis

A 73-year-old woman was initially diagnosed with ACC from a minor salivary gland of the floor of the mouth. At the time of diagnosis, the lesion involved the mandible right body and was staged as cT4N0M0. Histopathological examination confirmed the diagnosis, showing a cribriform growth pattern with perineural invasion (Figure 1).

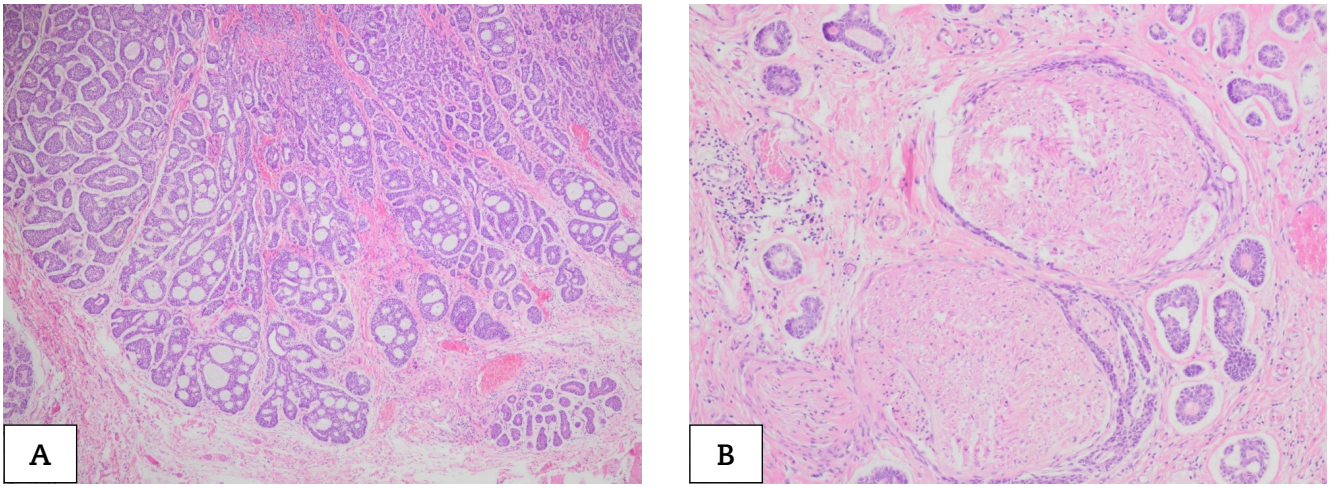

Figure 1. A: Adenoid cystic carcinoma. Cribiform pattern (HE 4x). B: Prominent perineural invasion (HE10x).

Primary treatment

The patient underwent local soft tissue wide resection together with anterior segmental mandibulectomy, followed by reconstruction with a free fibula flap. Given the advanced stage of the disease and the presence of adverse histopathological features, postoperative radiotherapy (RT) with 66 Gy following an intensity-modulated radiation therapy (IMRT) scheme was administered.

Follow-up

Post-operative follow-up revealed no signs of recurrence of malignancy in the control CT-scans, and clinical examination. Control biopsies, when performed, were related to inflammatory or infectious complications and showed no evidence of malignancy. Four years after the initial treatment, the patient underwent dental rehabilitation with osseointegrated implants placed in the fibula flap. This procedure led to osteoradionecrosis of the reconstructed mandible and consequent failure of the fibula flap, requiring a secondary mandibular reconstruction using a contralateral vascularized free fibula flap. Six months before the current presentation, the patient was diagnosed with symphyseal osteomyelitis involving the reconstructed mandibular region.

New lesion

Six years after completion of radiotherapy, the patient presented with progressive pain, swelling, and erythema in the floor of the mouth, associated with an infiltrated ulcer in the symphyseal region. Given the recent history of osteomyelitis and the clinical appearance of the lesion, an infectious or inflammatory process was initially suspected.

Due to persistent symptoms and local progression, an incisional biopsy was performed. Histopathological examination revealed mesenquimal proliferation compatible with a radiation-induced undifferentiated spindle cell sarcoma, represented in Figure 2. In the immunohistochemical analysis, Ki67 35 %, positivity against actine and calponin, and negativity for S100, epithelial (AE1-AE3, Cam 5.2 and p63), muscular (desmin and myogenin) and vascular markers (CD31, CD34, ERG) was demonstrated. A cervical-facial CT-scan showed signs of local recurrence around the VFFF, with a large mass associated with central necrotic areas. The mass measured 11 x 6-cm in its largest diameter, surrounding the VFFF from the symphysis to the right subcondylar region. It involved both lobes of the right parotid gland and the floor of the mouth bilaterally, infiltrating the mylohyoid muscle, both geniohyoid and genioglossus muscles, the right sternocleidomastoid and medial pterygoid muscles. In addition, there was bone infiltration of the fibula, the contralateral mandibular body and the right greater horn of the hyoid bone.

Outcome

The case was evaluated by a multidisciplinary team. Due to the extensive local involvement and the unresectable nature of the lesion, systemic chemotherapy was the treatment chosen. Despite treatment, the disease showed rapid progression, and the patient died four months after the diagnosis.

The main clinical events are summarized chronologically in Table I.

DISCUSSION

Radiation-induced spindle cell sarcoma (SCS) is a rare subtype of malignant soft tissue tumor characterized by uncertain differentiation and aggressive clinical behavior. Radiation induced malignancy represents a stochastic effect, without a safe dose threshold. The modified Cahan criteria are still frequently used for diagnosis, requiring

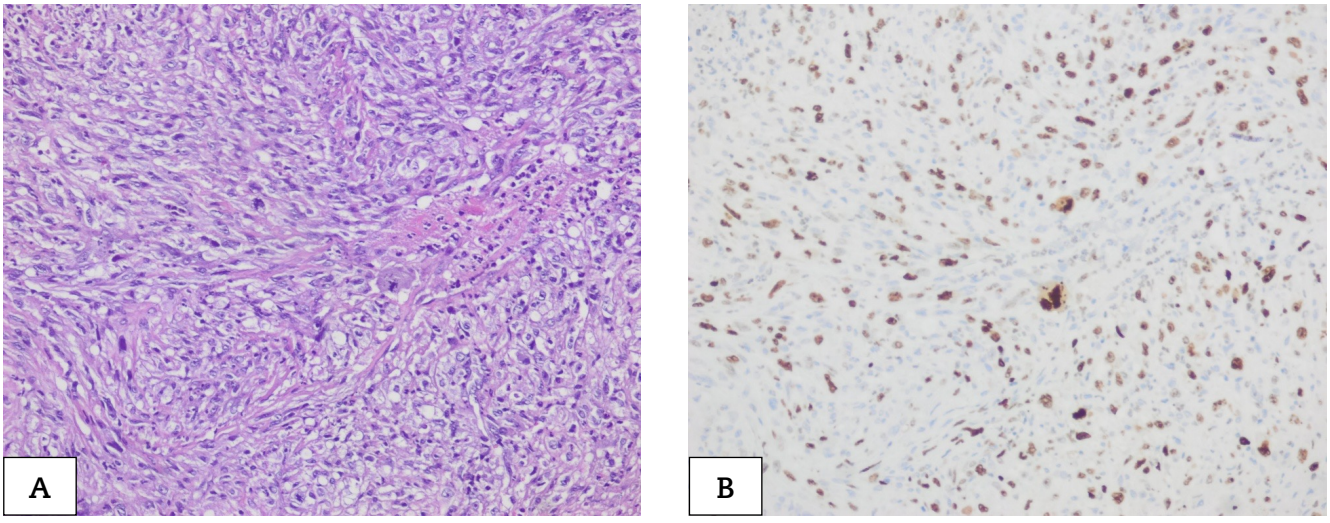

Figure 2. A: Radiation-induced spindle cells neoplasm with a storifom growth pattern and pleomorphic nuclei with atypical mitosis (HE 20x). B: Immunostainig for Ki-67.

Table I. Chronological summary of clinical events.

Time point (from initial oncological treatment)	Clinical event
Year 0	Diagnosis of ACC of the floor of the mouth (cT4N0M0) Tumor resection, reconstruction with free fibula flap and postoperative radiotherapy (IMRT, total dose 66 Gy)
Year 4	Dental rehabilitation with osseointegrated implants in the fibula flap Development of osteoradionecrosis with flap loss and secondary mandibular reconstruction with contralateral free fibula flap
Year 5.5	Diagnosis of symphyseal osteomyelitis in the reconstructed mandible
Year 6	**Diagnosis of radiation-induced undifferentiated spindle cell sarcoma**
Year 6 + 4 months	Death despite systemic chemotherapy

Table II. Radiation-induced spindle cell sarcoma cases in head and neck area.

Author, year	Age (yr) / Gender	Latency (yr)	Primary diagnosis	Radiation dose (Gy)	Site	Treatment	Outcome
Mark et al., 1994[6]	60/M	6.8	MPT	60	NA	S + RT + C	Living 4 years after dx
	75/M	11	SCC (true vocal cord)	60Gy + 36Gy	NA	NA	Living 9 years after dx
	57/F	7.5	LE nasopharynx	59,40Gy + 65Gy	NA	NA	Dead
Lagrange et al., 2000[7]	37/M	24	NA (Brain)	90	Bone skull	Partial S + C	Living 21 months after dx
Makimoto et al., 2007[8]	62/M	12	NPC	64	Skull base	No treatment	Died 13 months after dx
Khan et al., 2009[9]	24/M		R	40	Maxillary sinus	S	NA
Abrigo et al., 2009[10]	NA	10	NPC	NA	Maxillary sinus	NA	NA
	NA	9	NPC	NA	Sphenoid sinus	NA	NA
Debnam et al., 2012[11]	49/F	6.5	SC (sinonasal)	54	Orbital apex	C	Died 8 months after dx
	58/M	4.5	SCC (larynx)	68	Neck node	NA	Lost to follow up
	57/F	5.3	SA (upper eyelid)	NA	Orbital apex	S + C	Living 1 month after dx
	65/M	10	SCC (buccal mucosa)	NA	Retromolar tryigone	C	Living 16 months after dx
Uchimoto et al., 2022[12]	39/F	5.1	SCC (tongue)	60	Tongue	C	Living 2 years after dx
Present case	73/F	6	ACC (minor salivary gland)	66	Mandible	C	Died 4 months after dx

MPT: mixed parotid tumor. SCC: squamous cell carcinoma. LE: lymphoepithelioma. NPC: nasopharyngeal carcinoma. R: retinoblastoma. SC: schneiderian carcinoma. SA: sebaceus adenocarcinoma. ACC: adenoid cystic carcinoma. S: surgery. C: chemotherapy. RT: radiotherapy. NA: not available.

tumor development within a previously irradiated field after a latency period, histological distinction from the primary malignancy, and absence of the secondary tumor at the time of radiotherapy[3-5].

Within the spectrum of radiation-induced sarcomas of the head and neck, spindle cell sarcoma represents an exceptionally uncommon histological subtype. Coca-Pelaz et al. identified only a limited number of spindle cell sarcomas among radiation-induced head and neck sarcomas, while de Souza et al. reported no cases of spindle cell sarcoma in their systematic review of oral radiation-induced sarcomas. In addition, the most extensive systematic review to date of craniofacial radiation-induced sarcomas revealed that spindle cell sarcoma accounted for a mere 1.3 % of cases, classifying it as one of the rarest histological subtypes. It is interesting to note that this entity was also associated with a shorter mean latency period compared with other radiation-induced sarcomas. With an average interval of approximately seven years between radiotherapy and diagnosis, this is consistent with the relatively short latency observed in the present case[3-5]. Table II reports cases of SCS within the head and neck region, while Table III reports RIS following radiotherapy for ACC.

Table III. Radiation-induced sarcoma cases following radiotherapy for adenoid cystic carcinoma.

Author, year	Age (yr) / Gender	Latency (yr)	Primary diagnosis	Radiation dose (Gy)	Histologic type of RISHN	Site	Treatment	Outcome
Makimoto et al., 2007[8]	69/F	9	ACC	60	OS	Mandible	S	Died 11 months after dx
Belli et al., 2010[13]	36/F	8	ACC (Parotid gland)	NA	OS	Infra-temporal fossa	S + C	Died 5 months after dx
Debnam et al., 2012[11]	50/F	20	ACC (Parotid gland)	NA	OS	Mandible	C	Died 9 months after dx
Present case	73/F	6	ACC (minor salivary gland)	66	SCS	Mandible	C	Died 4 months after dx

ACC: adenoid cystic carcinoma. OS: osteosarcoma. SCS: spindle cell sarcoma. S: surgery. C: chemotherapy. NA: not available.

The pathogenesis of radiation-induced sarcomas is not fully understood. It has been established that ionizing radiation can induce persistent genomic damage and long-term genomic instability. Ultimately, these factors may lead to malignant transformation of mesenchymal cells within irradiated tissues. This process appears to be multifactorial and influenced by individual susceptibility, local tissue conditions, and additional modifying factors. These may partially explain the wide variability in latency periods reported in the literature[3-5].

The local tissue environment may be altered due to repeated surgical interventions, dental rehabilitation, osteoradionecrosis, flap failure, secondary reconstruction and chronic inflammatory processes. This may complicate clinical assessment and contribute to diagnostic delay in patients with extensive post-treatment changes. However, a direct causal relationship between reconstructive procedures and sarcoma development cannot be established.

Radiation-induced sarcomas often present with nonspecific signs and symptoms that overlap with common post-radiation complications, such as osteoradionecrosis or chronic infection. In the present case, the history of osteoradionecrosis and osteomyelitis lowered the initial suspicion of malignancy and contributed to diagnostic delay. The wide variability in latency periods and the poor survival outcomes reported for these tumours underscore the importance of maintaining a high index of suspicion and performing early biopsy of new or progressive lesions arising in previously irradiated and surgically altered fields.

High-grade transformation of salivary gland carcinomas should also be considered in the differential diagnosis, as it may present with sarcomatoid features in the histological analysis and an aggressive clinical course. However, in the present case, fulfilment of the Cahan criteria together with the histopathological and immunohistochemical findings supported a definitive diagnosis of radiation-induced SCS[1].

Due to the rarity and heterogeneity of radiation-induced sarcomas, clear treatment guidelines are lacking. Surgical resection with negative margins is generally considered the preferred approach when feasible, although this is often challenging in previously irradiated tissues. In unresectable cases, systemic therapy may be considered; however, outcomes remain poor.

CONCLUSION

Radiation-induced spindle cell sarcoma following treatment for adenoid cystic carcinoma is extremely rare. This case underscores the aggressive nature of radiation-induced sarcomas and the importance of maintaining a high index of suspicion for new lesions arising in previously irradiated and reconstructed tissues, where early diagnosis remains critical.

CONFLITS OF INTEREST

We have no conflicts of interest to disclose.

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