



Hyalinizing Clear Cell Carcinoma as a Secondary Malignancy in a Childhood Survivor of Rhabdomyosarcoma

Hilary Somerset*

Department of Pathology, University of Colorado School of Medicine, Colorado

Abstract

Secondary malignancies are an infrequent but well-known phenomenon whereby radiation treatment may predispose a patient to a subsequent malignant neoplasm years after his or her initial diagnosis. The head and neck is a common site for post radiation carcinomas including salivary gland tumors such as mucoepidermoid carcinoma (MEC), acinic cell carcinoma, and even (more recently described) mammary analogue secretory carcinoma (MASC). Hyalinizing clear cell carcinoma (HCCC) is a rare, low-grade carcinoma of the minor salivary glands with characteristic histologic and molecular findings. We report a case of HCCC of the lower lip arising as a secondary malignancy in a 40-year-old woman with a history of childhood rhabdomyosarcoma for which she received radiation therapy. To our knowledge, this report represents the first instance of HCCC being presented as a secondary head and neck malignancy. This case contributes to the spectrum of post radiation carcinomas and highlights the persistent risk of subsequent malignancies in childhood cancer survivors.

Keywords: Hyalinizing clear cell carcinoma; Rhabdomyosarcoma; Secondary malignancy; Radiation therapy

Introduction

Hyalinizing clear cell carcinoma is a rare minor salivary gland tumor characterized by a consistent *EWSR1-ATF1* fusion and distinct histology including some component of clear cells within a hyalinized stroma [1]. HCCC was first described by Milchgrub et al. [1] in 1994, although it was initially regarded as a diagnosis of exclusion in the absence of characteristic features of other clear-cell salivary gland tumors (e.g. mucoepidermoid carcinoma, epithelial-myoepithelial carcinoma, myoepithelial carcinoma, etc.). HCCCs are now recognized as a distinct pathologic entity with a *EWSR1-ATF1* fusion oncogene due to a t (12;22) [2]. Although this translocation is also described in other tumor types including some clear cell sarcomas and angiomatoid fibrous histiocytoomas, the exact breakpoints of *EWSR1* and *ATF1* are considered a unique and defining feature of HCCC [2].

HCCCs occur most commonly in the minor salivary glands of the oral cavity--especially the palate and tongue base--with perhaps a slight female predilection [3]. As the name implies, histologically HCCCs demonstrate nests and cords of clear cells within a hyalinized stroma with infiltrative borders and frequent perineural invasion [1,3]. Despite these latter features, HCCCs are typically low-grade carcinomas and tend to pursue an indolent clinical course with only rare reported metastases and/or aggressive features [1,4-5].

Thus far, HCCC has only been reported as a primary malignancy. Herein we report a case of HCCC arising in the post-radiation setting of a childhood survivor of rhabdomyosarcoma.

Case Presentation

A 40-year-old woman with a history of rhabdomyosarcoma of the left cheek / nose area (diagnosed at age 1 with a recurrence at age 8) presented to the ENT clinic with a one year history of a left lower lip mass. The patient reported that the mass may have slightly increased in size during her recent pregnancy, but was otherwise stable. MR Imaging of the face was non-diagnostic due to the patient's dental implants which obscured any interpretable views of the lips. On exam, the patient was found to have a firm, non-mobile lower lip mass measuring approximately 0.5 cm. The mass was excised and the postoperative course was unremarkable. Per the electronic medical records, the

OPEN ACCESS

*Correspondence:

Hilary Somerset, Department of Pathology, University of Colorado SOM
12605 East 16th Avenue, Mail Stop F768, Aurora, CO 80045, Colorado;
E-mail: hilary.somerset@ucdenver.edu

Received Date: 30 Sep 2016

Accepted Date: 26 Oct 2016

Published Date: 28 Oct 2016

Citation:

Somerset H. Hyalinizing Clear Cell Carcinoma as a Secondary Malignancy in a Childhood Survivor of Rhabdomyosarcoma. *Ann Clin Case Rep.* 2016; 1: 1166.

Copyright © 2016 Somerset H. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

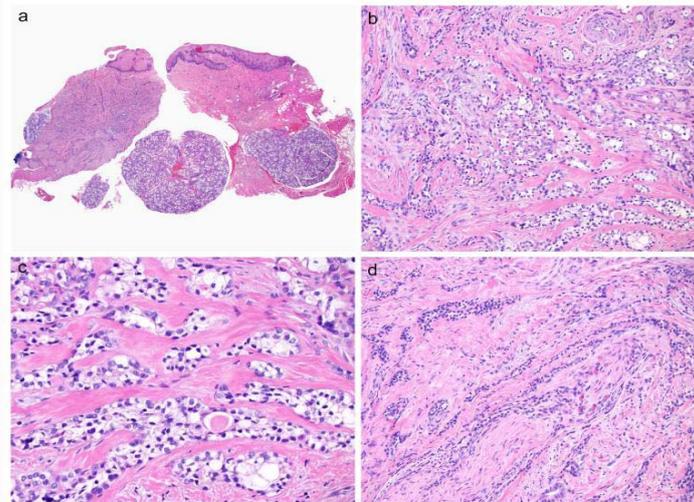


Figure 1: (a) HCCC adjacent to minor salivary glands with uninvolved squamous epithelium (hematoxylin and eosin x20). (b,c) Characteristic histology for HCCC with clear cells arranged in nests and cords within a hyalinized stroma (hematoxylin and eosin, x200, x400). (d) HCCCs are highly infiltrative tumors with frequent perineural invasion (hematoxylin and eosin x200).

patient's childhood rhabdomyosarcoma was managed with wide local excision and adjuvant therapy including chemotherapy and radiation therapy.

Results

Pathological evaluation

Sections show a highly infiltrative tumor located adjacent to minor salivary glands with extension into underlying skeletal muscle (Figure 1A). The overlying squamous epithelium is uninvolved. The tumor is characterized by nests and cords of monomorphic polygonal cells with clear (to pale eosinophilic) cytoplasm in a densely hyalinized stroma (Figure 1B and C). Mitoses are inconspicuous. Perineural invasion is present, but there is no lymph-vascular invasion (Figure 1D). No high-grade features such as necrosis, anaplasia or increased mitotic activity were seen. Attempts to retrieve the slides from the original rhabdomyosarcoma were unsuccessful, as materials were no longer available.

Molecular evaluation

Fluorescence in situ hybridization (FISH) for *EWSR1* was performed on the lip mass with a *EWSR1* dual-color break-apart 22q12 probe (Abbott Molecular, Des Plaines, IL) where the 5' *EWSR1* signal was labeled with orange and the 3' *EWSR1* signal was labeled with green. One hundred tumor nuclei were evaluated and split signals defined as 5' and 3' signals observed at a distance greater than one-time signal width. Fused (i.e. yellow) signals in uninvolved cells served as an internal control and the FISH was considered positive if greater than 20% of nuclei demonstrated a split or isolated 5' signal. The FISH was positive for a *EWSR1* rearrangement (Figure 2).

Discussion

Despite ongoing advances in cancer therapeutics, the unfortunate paradox of cancer treatment persists: that is, it can be both curative and oncogenic. Specifically, secondary malignancies are an uncommon but important complication of radiation therapy. Meadows et al. [6] recently reported the thirty-year cumulative incidence of second malignant neoplasms in childhood survivors of cancer as 9.3%, a figure that remained elevated even when age-matched controls independently reached ages associated with an increased likelihood

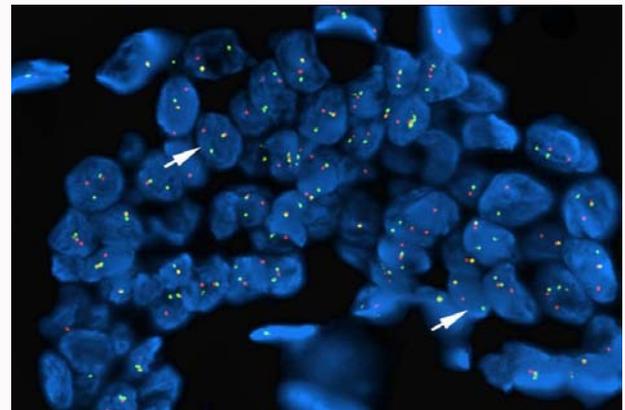


Figure 2: A FISH dual-color break-apart probe confirmed the present of *EWSR1* (22q12) gene rearrangement. The split orange and green signals (arrows) indicate a positive break-apart pattern. Images courtesy of Dr. Raja Seethala at UPMC.

of cancer [6].

This enduring risk underscores the importance of judicious use of radiation therapy especially in children as well as the need for ongoing surveillance and follow-up of this unique patient population (i.e. childhood cancer survivors) even well into adulthood.

In our case the patient was diagnosed with a childhood rhabdomyosarcoma for which she received radiation therapy. She then presented over thirty years later with a second malignancy. This experience is congruent with the findings from the Childhood Cancer Survivor Study Cohort, as the cohort demonstrated: 1) a greater risk for female versus male survivors, 2) a four-fold higher risk of carcinoma than expected compared to the general population, and 3) head and neck carcinomas (especially the parotid gland) as among the most common sites for carcinomas [6].

Among head and neck tumors, several salivary gland tumors have been previously documented as secondary malignancies including mucoepidermoid carcinoma, acinic cell carcinoma, and more recently mammary analogue secretory carcinoma [7-10]. To our knowledge, however, heretofore hyalinizing clear cell carcinoma has

not been implicated as a secondary malignancy.

The purported mechanism of carcinogenesis for secondary malignancies involves chromosomal rearrangements between nearby locations and break-points induced by ionizing radiation, a phenomenon that has been previously described in head and neck tumors including papillary thyroid carcinoma (PTC) and mucoepidermoid carcinoma [11]. It is not surprising then, that many of the second malignancies (e.g. PTC, MEC, MASC) tend to harbor a defining translocation, as was seen in our case. Although we cannot firmly prove that this HCCC is radiation-induced, it does meet Cahan criteria in that it: 1) arose within the radiation field, 2) occurred greater than five years following the original receipt of radiation, and 3) exhibited different histology than the original diagnosis [12]. Also, the patient did not have any known cancer predisposition syndromes. Finally, while we acknowledge that we can't fully exclude a coincidental occurrence of sarcoma and carcinoma in our patient, we feel that the rarity of each diagnosis, the novel molecular changes, and the history of radiation therapy make a causal relationship much more plausible.

In summary, we expand the breadth of secondary head and neck malignancies by describing for the first time the occurrence of HCCC, a rare salivary gland tumor, in a childhood survivor of rhabdomyosarcoma. This case emphasizes how novel fusion transcripts (i.e. *EWSR1-ATF1*) may result after treatment of the primary cancer, and reminds us that the risk of secondary malignancy remains relevant even decades after the initial diagnosis. Although certain types of head and neck tumors are well recognized to occur after receipt of radiation therapy to the region, there is always a level of uncertainty when new tumor types appear to be radiation-induced. We document this current case of HCCC to make other investigators aware of the possibility that HCCC may also radiation-induced and to provide the precedent case.

Acknowledgement

Special thanks to Dr. Raja Seethala at the University of Pittsburgh for his expert consultation including FISH studies and images.

References

1. Milchgrub S, Gnepp DR, Vuitch F, Delgado R, Albores-Saavedra J. Hyalinizing clear cell carcinoma of salivary gland. *Am J Surg Pathol*. 1994; 18: 74-82.
2. Antonescu CR, Katabi N, Zhang L, Sung YS, Seethala RR, Jordan RC. *EWSR1-ATF1* fusion is a novel and consistent finding in hyalinizing clear-cell carcinoma of salivary gland. *Genes Chromosomes Cancer*. 2011; 50: 559-570.
3. Weinreb I. Hyalinizing clear cell carcinoma of salivary gland: a review and update. *Head Neck Pathol*. 2013; 7 Suppl 1: S20-29.
4. O'Regan E, Shandilya M, Gnepp DR, Timon C, Toner M. Hyalinizing clear cell carcinoma of salivary gland: an aggressive variant. *Oral Oncol*. 2004; 40: 348-352.
5. Jin R, Craddock KJ, Irish JC, Perez-Ordóñez B, Weinreb I. Recurrent hyalinizing clear cell carcinoma of the base of tongue with high-grade transformation and *EWSR1* gene rearrangement by FISH. *Head Neck Pathol*. 2012; 6: 389-394.
6. Meadows AT, Friedman DL, Neglia JP, Mertens AC, Donaldson SS, Stovall M, et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. *J Clin Oncol*. 2009; 27: 2356-2362.
7. Kaste SC, Hedlund G, Pratt CB. Malignant parotid tumors in patients previously treated for childhood cancer: clinical and imaging findings in eight cases. *AJR Am J Roentgenol*. 1994; 162: 655-659.
8. Cheuk DK, Shek TW, Chan GC, Lau YL, Ha SY, Chiang AK. Parotid acinar cell carcinoma in a long-term survivor of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2008; 50: 636-639.
9. Tugcu D, Akici F, Aydogan G, Salcioglu Z, Akcay A, Sen H, et al. Mucoepidermoid carcinoma of the parotid gland in childhood survivor of acute lymphoblastic leukemia with need of radiotherapy for treatment and review of the literature. *Pediatr Hematol Oncol*. 2012; 29: 380-385.
10. Woo J, Seethala RR, Sirintrapun SJ. Mammary analogue secretory carcinoma of the parotid gland as a secondary malignancy in a childhood survivor of atypical teratoid rhabdoid tumor. *Head Neck Pathol*. 2014; 8: 194-197.
11. Nikiforova MN, Stringer JR, Blough R, Medvedovic M, Fagin JA, Nikiforov YE. Proximity of chromosomal loci that participate in radiation-induced rearrangements in human cells. *Science*. 2000; 290: 138-141.
12. CAHAN WG, WOODARD HQ. Sarcoma arising in irradiated bone; report of 11 cases. *Cancer*. 1948; 1: 3-29.