Androgen Receptor Expression in Primary Nonsquamous Cell Rare-Variant Carcinomas of the Head and Neck

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Abstract

Objective. Androgen receptor (AR) is a diagnostic immunohistochemical marker for salivary gland duct carcinoma (SDC), but other nonsquamous cell head and neck carcinomas (NSCCs) may also express it. The aim of this preliminary study was to investigate the immunohistochemical expression of AR in rare head and neck NSCCs.

Study Design. Retrospective analysis of histologic records.

Setting. A large community hospital.

Subjects and Methods. Twenty-seven patients with NSCC were selected (21 men, 6 women; average age, 69 years). Exclusion criteria were histologically confirmed primary and metastatic head and neck squamous cell carcinomas and thyroid carcinomas. AR immunohistochemistry was done on formalin-fixed, paraffin-embedded tissue blocks.

Results. Variable AR expression was found in 5 of 27 (25%) cases of NSCC. All 7 patients with SDC showed intense and extensive positive immunoreactivity. Of 27 NSCC tumors, 15 (56%) had negative staining.

Conclusion. In the head and neck, expression of AR is not limited to SDCs; other NSCCs also express it. When surgery or radiotherapy is not appropriate for recurrent or metastatic head and neck NSCC, palliative chemotherapy offers poor results. Antiandrogen therapy is well tolerated and is much less toxic than chemotherapy. Since androgen deprivation therapy has been used against SDCs, this therapy may theoretically be used in a small subset of head and neck NSCCs.

Keywords

head and neck, nonsquamous cell carcinoma, androgen receptor, immunohistochemistry, preliminary study

Androgen receptor (AR) is a well-known reliable diagnostic immunohistochemical marker for salivary gland duct carcinoma (SDC),[1-5] a highly malignant neoplasm with an extremely poor prognosis. The 5-year survival rates of all patients affected by SDC have been reported to be 0% to 30%.[6-9] Androgen deprivation-based therapy (ADT) has recently been proposed in the treatment of advanced-stage SDC.[5,10-15]

The mainstay of primary treatment for locoregional SDC and other head and neck nonsquamous cell carcinomas (NSCCs) is surgery; in the presence of high-grade tumors, positive margins, or other high-risk features, local control is improved with adjuvant radiotherapy.[16-18] For inoperable cases, radiotherapy alone is used but with a lower local control rate.[19-21] The addition of chemotherapy to adjuvant radiotherapy has not been shown to confer an advantage.[22]

As the incidence of rare variants of NSCC versus squamous cell carcinoma is low, these cancers are understudied. Consequently, discovering new immunohistochemical markers could theoretically contribute to developing more focused, efficient, and possibly less toxic target-based therapies.

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Other than sporadic reports of AR-positive head and neck NSCC,[23-25] to our knowledge, there is no systemic evaluation of AR expression in a series of these tumors. In this preliminary study, we investigate the immunohisto-chemical expression of AR in 27 patients with nonsquamous cell rare-type carcinomas of the head and neck.

Methods

Twenty-seven patients with NSCC in the head and neck region were selected from the pathology files of Queen Alexandra Hospital, Portsmouth, United Kingdom. Since this was a retrospective study aimed to ameliorate the diagnostic and therapeutic services, no institutional review board and/or ethics committee approval was necessary.

Exclusion criteria were histologically confirmed primary and metastatic squamous cell carcinomas of the head and neck and primary and metastatic thyroid carcinoma. Rare and understudied subtypes of head and neck NSCCs were included in the study. A total 35 cases of NSCCs were reviewed, and among these, 20 cases were selected. We tried to select cases that, in case of metastasis or recurrences, would represent a therapeutic challenge for head and neck surgeons and oncologists. According to the pathology file records, some subtypes were excluded from the study due to unavailability of paraffin-embedded neoplastic tissue. To compare the status of immunostaining, 7 cases of SDCs were also included in the study, owing to their well-known positive immunoreactivity with AR.

Archived histologic hematoxylin and eosin–stained slides were reviewed from all study cases. Slides containing the best areas of tumor representation were selected for the immunohistochemical study. Corresponding formalin-fixed, paraffin-embedded tissue blocks were retrieved from the archives, and serial 3-μm sections were cut. Sections were mounted onto adhesive slides (Surgipath Snowcoat; Leica, Newcastle upon Tyne, UK) and dried at 65°C for 15 minutes. Each slide included a positive control tissue (prostate). Each series of sections was stained with AR antibody (rabbit monoclonal antibody, clone EP120; CellMarque, Rocklin, California) on a Leica Bond III automated immunostaining platform with Leica Bond Polymer Refine Detection and a DAB chromogen (DS9800; Leica), based on a dilution of 1:200 for 15 minutes at room temperature, following on-board heat-induced epitope retrieval with Leica ER2 solution (AR9640; Leica). A negative control, where the primary antibody was omitted, was included in the run. Immunostaining for AR was assessed by 2 pathologists (S.R. and C.M.). Only positive nuclear staining was graded as a positive result. Scores were assigned according to percentage of stained lesional cells and intensity of staining. The cases were classified as negative (staining score, 0) or positive ($\geq$1; **Table 1**).

Results

Twenty-one men and 6 women were included. The mean age was 69 years (range, 45-90 years). The staining was homogeneous for men and women.

Table 1. Scoring of the Immunohistochemical Findings.

Finding	Score
Positive lesional cells, %	
0	0
1-25	1+
26-50	2+
51-80	3+
81-100	4+
Staining pattern	
None	0
Weak	1+
Moderate	2+
Intense	3+

All 7 SDCs, including the in situ type, showed positive nuclear staining. Five NSCCs also showed nuclear immunoreactivity with AR: 1 was a high-grade carcinoma as a component in carcinoma ex pleomorphic adenoma of the submandibular gland; 1 was high-grade "duct-like" carcinoma of the ocular lacrimal drainage system; 2 were not otherwise specified (NOS) high-grade carcinomas involving the entire eye globe and submandibular gland; and 1 was tongue intestinal-type adenocarcinoma.

The AR expression was intense and present in almost 100% of cells in all SDCs (including the in situ subtype), in high-grade carcinoma ex pleomorphic adenoma (case 8; see cases in **Table 2**), and in "duct-like" carcinoma of the lacrimal drainage system (case 11; **Figure 1A**). Expression was also intense and present in approximately 80% of malignant cells in intestinal-type adenocarcinoma of tongue (case 12; **Figure 1B**) and in approximately 70% (**Figure 1C**) and 15% (**Figure 1D**) of high-grade NOS carcinomas of the submandibular gland and orbit, respectively (cases 9 and 10).

All patients with AR-positive NSCCs had surgery, followed by conventional radiotherapy, chemotherapy, or both. No patient was offered ADT. The remaining 15 NSCCs had negative AR staining: 1 parotid basal cell adenocarcinoma, 1 parotid mammary analogue secretory carcinoma, 2 parotid epithelial-myoepithelial carcinomas, 2 high-grade NOS carcinomas of the parotid and submandibular gland, 3 parotid acinic cell carcinomas (1 conventional type, 1 papillary-cystic, 1 with rich lymphoid stroma), 2 solid-variant adenoid cystic carcinomas of upper gum and submandibular gland, 2 intermediate-grade mucoepidermoid carcinomas of the base of tongue, and 2 cylindrical cell (transitional) carcinomas of nasal mucosa and nasolacrimal duct. The summary of the results, including the status of regional lymph nodes and follow-up, is shown in Table 2. The range of follow-up was 8 to 60 months.

Discussion

This study confirms that AR is a reliable immunohistochemical marker for diagnosis of SDC. However, our results

Table 2. Summary of the Results.

Case	Age, y	Sex	Site	Diagnosis	AR	Score[a]	RLN[b]	Outcome, mo
1	78	M	R parotid	SDC	+	4+3	+	DD, 60
2	87	M	L parotid	SDC	+	4+3	+	DD, 36
3	71	M	R parotid	SDC	+	4+3	−	DD, 40
4	75	M	R parotid	SDC	+	4+3	−	DU, 32
5	79	F	R parotid	SDC	+	4+3	+	DD, 20
6	81	M	L parotid	SDC	+	4+3	−	LF, −
7	66	M	L parotid	SDC in situ	+	4+3	−	AN, 10
8	52	M	R submandibular	HG carcinoma[c]	+	4+3	−	AD, 30
9	80	M	L submandibular	HG NOS carcinoma	+	3+3	+	DD, 26
10	90	M	L orbit	HG NOS carcinoma	+	1+3	+	DD, 22
11	56	M	LDS	HG carcinoma ("duct-like")	+	4+3	−	DU, 10
12	58	M	Tongue	Intestinal-type adenocarcinoma	+	4+3	+	AD, 40
13	77	M	R parotid	BCC	−	0+0	−	AN, 20
14	52	M	L parotid	MASC	−	0+0	−	AN, 26
15	45	M	L parotid	EMC	−	0+0	−	AN, 20
16	73	M	R parotid	EMC	−	0+0	−	AN, 18
17	89	M	R parotid	HG NOS carcinoma	−	0+0	+	AD, 20
18	76	M	L submandibular	HG NOS carcinoma	−	0+0	−	AN, 28
19	72	F	R submandibular	AdCC	−	0+0	+	AD, 15
20	63	M	Upper gum	AdCC	−	0+0	−	AN, 18
21	69	F	Base of tongue	MEC	−	0+0	−	AN, 15
22	69	F	Base of tongue	MEC	−	0+0	−	AN, 10
23	53	F	R parotid	ACC conventional	−	0+0	−	AN, 16
24	62	F	R parotid	ACC with lymphoid stroma	−	0+0	−	AN, 20
25	85	M	L parotid	ACC papillary cystic	−	0+0	−	AN, 22
26	46	M	Nasal mucosa	CCC	−	0+0	−	AD, 8
27	60	M	Nasolacrimal duct	CCC	−	0+0	−	AD, 12

Abbreviations: ACC, acinic cell carcinoma; AD, alive with disease; AdCC, adenoid cystic carcinoma; AN, alive with no disease; AR, androgen receptor status; BCC, basal cell carcinoma; CCC, cylindrical (transitional) cell carcinoma; DD, dead with disease; DO, dead for unrelated disease; EMC, epithelial-myoepithelial carcinoma; HG, high grade; L, left; LDS, lacrimal drainage system; LF, lost for follow-up; MASC, mammary analogue secretory carcinoma; MEC, mucoepidermoid carcinoma; NOS, not otherwise specified; R, right; RLN, regional lymph node; SDC, salivary gland duct carcinoma.
[a]Score is based on percentage of stained lesional cells and intensity of staining.
[b]Status of regional lymph nodes (+, metastasis).
[c]In carcinoma ex pleomorphic adenoma.

showed that in the head and neck, AR expression is not limited to this malignancy and other NSCCs may express it.

The intensity and percentage of tumor cell staining were different among cancers. While SDCs showed intense and extensive expression, the range of positive staining changed from 15% to 80% in other types of carcinoma. These data should not be ignored, because small biopsies could generate a false-negative result. The AR gene is activated in SDC as in prostatic and breast carcinomas.[1-4,26,27] Interestingly, normal salivary gland parenchyma does not express AR,[28] in contrast to the epithelial component of normal prostate and breast parenchyma. Mitani et al showed that, in contrast to prostatic carcinoma, there is no AR gene amplification in SDC.[13]

Due to AR expression in SDC, some authors suggested that the AR-mediated autocrine growth pathway—consisting of epidermal growth factor receptor and its ligand transforming growth factor α, which is involved in prostate tumorigenesis—might also be involved in the pathogenesis of SDC.[12] Based on this speculation and the assumption that there is no AR gene amplification in NSCCs, this pathway might be involved in the carcinogenesis of other types of NSCC.

In the context of recurrent or metastatic head and neck NSCC, when surgery or radiotherapy is not appropriate, palliative chemotherapy achieves disappointing response rates of 10% to 70%, with duration of response only a few months.[29] Much less toxic than chemotherapy, antiandrogen therapy is well tolerated, with the optimal dose known from its established role in prostate cancer therapy. Interestingly, case series and single-case reports in metastatic head and neck NSCC indicate responses to ADT for about 50% of patients, with duration around 12 months[30,31] and a case report of a complete response.[32] A retrospective study showed an impressive objective response rate of 65% when
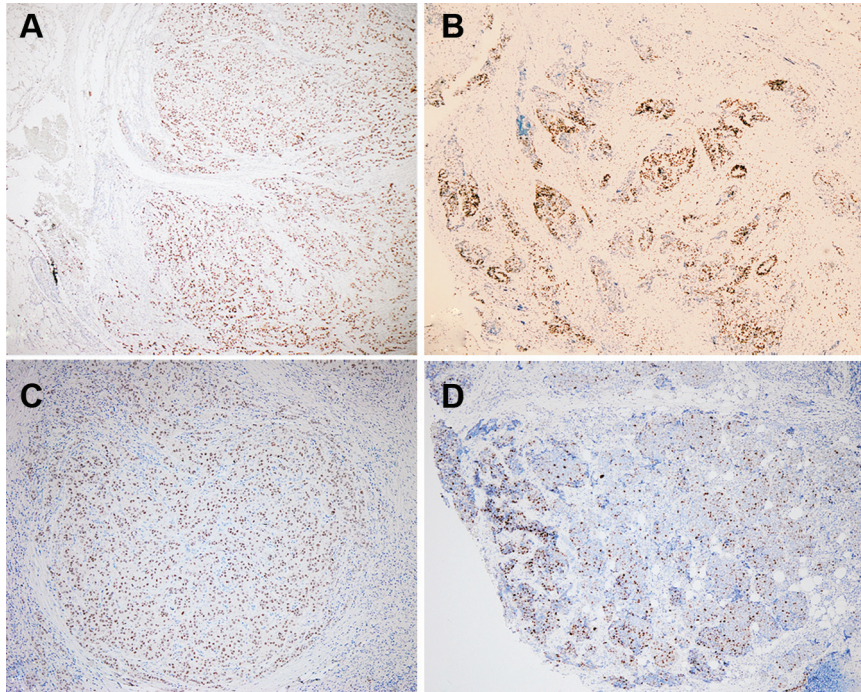
Figure 1. Immunohistochemistry shows intense positive nuclear staining with androgen receptor: A, carcinoma of the lacrimal drainage system (case 11); B, intestinal-type adenocarcinoma of tongue (case 12); C, submandibular gland high-grade NOS carcinoma (case 9); D, high-grade NOS carcinoma of orbit (case 10). NOS, not otherwise specified.

patients with SDC were treated uniformly with bicalutamide and triptorelin.[33]

In the noncurable setting, with quality of life a primary goal, ADT therefore gives a significant advantage over chemotherapy in terms of decreased toxicity, without sacrificing efficacy. A logical extension to this role is the addition of ADT to radiotherapy, particularly when used as primary therapy, in the hope of achieving a higher chance of local control. Indeed, there is a reported complete response following radiotherapy and ADT.[11]

Positive AR immunostaining is not only important as a diagnostic marker but also potentially crucial in determining therapeutic strategies. Since ADT therapy has been used against SDCs,[5,10-15] this therapy may theoretically be used in other NSCCs.

The findings of this preliminary study suggest that immunohistochemical analysis of AR could be useful in advanced stages and recurrences of head and neck NSCCs and may guide ADT in a small subset of these malignancies.

Author Contributions

Siavash Rahimi, design of the work, acquisition of data, analysis, interpretation of data, revising the paper critically, final approval, accountable for all aspects of the work; **Katherine L. Bradley**, interpretation of data, revising the paper critically, final approval, accountable for all aspects of the work; **Iolia Akaev**, data analysis, interpretation of data, revising the paper critically, final approval, accountable for all aspects of the work; **Carla Marani**, data analysis, interpretation of data, revising the paper critically, final approval, accountable for all aspects of the work; **Chit Cheng Yeoh**, interpretation of data, revising the paper critically, final approval, accountable for all aspects of the work; **Peter A. Brennan**, interpretation of data, revising the paper critically, final approval, accountable for all aspects of the work.

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