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Rhabdomyosarcoma of the adult head and neck: a clinicopathological and DNA ploidy study

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Abstract

We investigated the DNA ploidy patterns in thirteen primary and four recurrent rhabdomyosarcomas of the head and neck from thirteen adult patients and correlated the findings with other clinicopathological factors and clinical outcome. Twelve (92.7 per cent) of the primary neoplasms manifested an aneuploid DNA pattern, five had more than one stemline, and one neoplasm displayed a diploid DNA pattern. All recurrent lesions were DNA aneuploid with DNA indices (DIs) corresponding to their primary neoplasms. No correlation between the ploidy pattern and histological subtypes, tumour location, clinical stage and patient's clinical course was found. In this study, only two patients were long-term survivors. Both patients had stage I neoplasms that were located in non-parameningeal sites which manifested an alveolar histological pattern. Our data indicate that adult rhabdomyosarcomas of head and neck are preponderantly DNA aneuploid and are highly aggressive malignant neoplasms. Our results also suggest that tumours which are low stage and in a non-parameningeal location may pursue a less aggressive course.

Key words: Rhabdomyosarcoma; Flow cytometry; DNA

Introduction

Rhabdomyosarcoma is the most common paediatric mesenchymal neoplasm. It comprises approximately 50 per cent of all soft tissue sarcomas in this age group (Donaldson, 1989). In the Intergroup Rhabdomyosarcoma Study–I (IRS–I), more than one-third of rhabdomyosarcomas were located in the head and neck, distributed nearly evenly in orbital (10 per cent), parameningeal (14 per cent) and non-parameningeal–non-orbital (13 per cent) locations (Sutow *et al.*, 1982; Newman and Rice, 1984).

Rhabdomyosarcomas in adults are rare (Lloyd *et al.*, 1983; Donaldson, 1989; Nakhleh *et al.*, 1991). Accordingly, published data regarding their natural history, prognostic parameters and response to treatment are sparse. Available data, however, indicate that rhabdomyosarcomas in adults are more aggressive in their behaviour than those in children (Lloyd *et al.*, 1983; Donaldson, 1989; Prestidge and Donaldson, 1989; Nakhleh *et al.*, 1991).

Studies of the flow cytometric DNA content in rhabdomyosarcomas and other related childhood neoplasms suggest a utility for such analysis in the clinical assessment of these neoplasms (Look *et al.*, 1982; Look *et al.*, 1984; Gansler *et al.*, 1986; Schmidt *et al.*, 1986; Boyle *et al.*, 1988; Molenaar *et al.*, 1988; Kowal-Vern *et al.*, 1990; Shapiro *et al.*, 1991). In the present study, we have investigated the cellular DNA ploidy content of rhabdomyosarcomas of the head and neck in adult patients and correlated the DNA content with clinicopathological features and outcome. To our knowledge, a similar study has not been done before.

Materials and methods

Thirteen rhabdomyosarcomas, with available tissue blocks from patients 18 years or older, accessioned at the Department of Pathology, M.D. Anderson Cancer Center from 1960–1980, formed the basis for this study. Tumour size and site were obtained from the surgical pathology report. Demographic data, treatment modalities and follow-up information were derived from the patients' medical records. Clinical stage at the time of diagnosis was defined according to the Intergroup Rhabdomyosarcoma Study–I recommendation (Maurer, 1975).

Haematoxylin and eosin-stained sections from all neoplasms were available for histological evaluation. Two to nine slides (average four slides) per tumour were reviewed.

Immunohistochemistry

Immunohistochemical studies were performed on formalin-fixed, paraffin-embedded tissues using the avidin–biotin–peroxidase complex (ABC) method of Hsu *et al.* (1981). To enhance the immunostaining, sections were incubated with 0.1 per cent protease (Type XIV, Sigma Chemical, St Louis, MO) in phosphate buffer pH 7.6) for 30 minutes. Sections were stained with two anti-desmin mouse monoclonal antibodies i.e. D33 (Dako Corp., Santa Barbara, CA; 1:100 dilution) and DER-11 (Dako Corp.; 1:20 dilution) and also with HHF-35 anti-muscle specific actin (Enzo Biochem, New York, NY; 1:3000 dilution),

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anti-vimentin (V9, Dako; 1:30 dilution), and anti-smooth muscle actin (Sigma; 1:1000 dilution) monoclonal antibodies. Sections were also stained with a 'cocktail' of two anti-keratin monoclonal antibodies (AE1/AE3, Boehringer-Mannheim, Indianapolis, IN; 1:300 dilution) which recognizes a wide range of low and high molecular weight keratin peptides. The immunoperoxidase reaction was visualized using 3-amino-9-ethylcarbazol as chromogen. The slides were counterstained with Mayer's haematoxylin. Known positive and negative control tissue sections were used in order to determine the specificity of the immunoreaction. Details of the immunostaining procedure have been described elsewhere (Ordóñez *et al.*, 1988).

Flow cytometry

One to four tissue blocks of each neoplasm were separately analysed. Nuclear suspensions of the neoplasms were prepared using a modified version (McLemore *et al.*, 1990) of the method of Hedley (1983). In each block selected for analysis, at least 75 per cent of the tissue was neoplastic. Blocks of the neoplasm with more than 10 per cent necrosis were avoided. Lesser necrotic areas were mapped and non-necrotic tissue was re-embedded for flow cytometric analysis. Specimens were analysed on an Epics Profile I flow cytometer (Epics Division, Coulter Electronics, Hialeah, FL) equipped with an argon ion laser operating at 488 nm, with a 610 long pass filter and 488 band pass. Flow rates were adjusted to the count of approximately 75 nuclei per second. Peak *versus* integral signals were employed to exclude doublets.

Cytospin slides were prepared from a 10^6 nuclei/ml concentration (unexposed to RNAse) and stained with Wright–Giemsa. The slides were reviewed to confirm the presence of tumour nuclei as well as to monitor the quality of processing. In each sample, at least 10 000 nuclei were evaluated. The DNA histograms were analysed using the boxogram gating procedure of Johnston *et al.* (1978). Non-neoplastic tissue was used as the biological diploid standard and the first G_0/G_1 population was used to denote the diploid stemline.

The DNA index (DI) was defined as the ratio of the peak channel number of the test sample to the peak channel of the normal diploid control. By definition, the DI of diploid population is 1.0. A tumour was considered aneuploid when a distinct second G_0/G_1 peak, accounting for at least 10 per cent of the cells analysed, was present (or any number of such separate peaks).

Results

The clinicopathological and flow cytometric DNA findings and patients' outcome are presented in Table I.

The patient population was made up of eight males and five females who ranged in age from 18 to 77 years (mean 31.8 years) at the time of histological diagnosis. The locations of the neoplasms were as follows: orbit, one; parameningeal sites, five; non-parameningeal locations, seven. In eight tumours, the size was known and ranged from 3 to 15 cm (average 8.0 cm).

Histopathology

Histopathologically, nine neoplasms were alveolar and

TABLE I
CLINICOPATHOLOGICAL FEATURES AND FLOW CYTOMETRIC DNA CONTENT OF HEAD AND NECK RHABDOMYOSARCOMAS IN ADULTS

Case number	Age	Sex	Site	Stage	Size	Histological subtype	Treatment	Immunohistochemistry				Flow cytometry			
								Desmin							
								(DER-11)	(D33)	(MSA)	(VIM)	DI	S%	Follow-up (months)
1	32	M	Neck soft tissue	II	12 cm	Alveolar	S, RT,	3+	4+	4+	0	1.32, 2.35	11	5, DOD
2	23	F	Floor of mouth	I	3 cm	Embryonal	S, CT, RT	2+	3+	3+	3+	2.67, 2.53	8	78, DOD
3	77	M	Paranasal sinus	III	6 cm	Alveolar	S, CT, RT	1+	4+	1+	3+	1.77, 3.30	8	31, DOD
4	28	M	Orbit	III	5 cm	Alveolar	S, CT, RT	1+	4+	4+	3+	2.34, 2.75	12	20, DOD
5	34	M	Neck soft tissue	II	9 cm	Alveolar	S, CT, RT	1+	2+	1+	4+	1.14, 1.85	5	15, DOD
6	18	F	Maxillary sinus	III	NK	Alveolar	S, RT,	1+	2+	3+	4+	1.25, 3.25	6	24, DOD
7	22	M	Ethmoid sinus	III	NK	Embryonal	RT	0	1+	1+	0	2.00	12	2, DOD
8	19	F	Neck soft tissue	II	15 cm	Alveolar	S, RT,	1+	1+	2+	4+	1.00	5	6, DOD
9	27	M	Paranasal sinus	III	10 cm	Embryonal	S, RT	2+	0	2+	1+	1.41	3	46, DOD
10	45	M	Cheek	I	5 cm	Alveolar	S, CT, RT	0	1+	1+	4+	2.00	9	132
11	70	F	Paranasal sinus	III	NK	Embryonal	S, CT, RT	2+	1+	1+	4+	1.23	11	23, DOD
12	18	M	Buccal mucosa	I	NK	Alveolar	S, RT	1+	4+	2+	0	2.93	6	300
13	19	F	Soft tissue mandible	II	BX	Alveolar	S, CT	1+	1+	1+	0	1.87	8	15, DOD

S: surgery; CT: chemotherapy; RT: radiation therapy; NK: not known; BX: biopsy; DOD: died of disease; 0: no reaction; 1+: ≤ 25+ per cent reactivity in tumour cells; 2+: 26–50 per cent; 3+: 51–75 per cent; 4+: ≥ 75 per cent; DI: DNA index; S%: S-phase; MSA: muscle specific actin; VIM: vimentin.

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four were embryonal subtypes. Two neoplasms, (numbers 2 and 7) with an embryonal appearance, also manifested focal areas of an alveolar phenotype.

Immunohistochemistry

All 13 tumours stained with HHF-35 anti-muscle specific actin monoclonal antibody. Twelve tumours reacted with D33 anti-desmin antibody and 11 with DER-11. The only tumour that did not immunoreact with D33, reacted with DER-11. In general, a larger number of tumour cells stained with D33 than with the DER-11 anti-desmin antibody. Nine neoplasms stained for anti-vimentin, while none reacted with keratin or anti-smooth muscle actin antibodies.

Treatment and outcome

All patients but one had some form of surgical excision. In that particular patient (case no. 7), a biopsy was performed and the patient was subsequently treated with radiotherapy. Of the surgically-treated patients, three underwent complete surgical excision with free margins. In nine patients, the tumours were incompletely excised. Four patients received post-operative radiotherapy and six were treated with combined post-operative chemo- and radiotherapy.

Clinical staging and outcome

Three patients were stage I, four were stage II, and six were stage III. The follow-up periods ranged from two to 300 months (average 53.6 months). Eleven patients died of their disease and two (cases no. 10 and no. 12) are alive without evidence of disease 132 and 300 months after diagnosis. Both patients had stage I neoplasms which were located in non-parameningeal sites. Histologically, they presented an alveolar pattern.

DNA content

Eleven neoplasms were DNA aneuploid, one neoplasm was DNA diploid, and one had a tetraploid DNA content. Five of the aneuploid neoplasms manifested more than one aneuploid DNA stemline. There were no apparent correlations between the DNA ploidy status and tumour location, histological subtype, clinical stage and patient outcome.

The proliferative fractions ranged from three to 12 per cent with a mean of 8.0 per cent. There were no apparent correlations between the proliferative fraction and other clinicopathological parameters.

Discussion

Rhabdomyosarcoma is a histologically diverse and preponderantly paediatric malignant soft tissue neoplasm. Tumours in head and neck locations comprise approximately 40 per cent of all cases in the paediatric age group (Sutow *et al.*, 1982; Newman and Rice, 1984; Donaldson, 1989). In this age group, the clinical outcome has dramatically been improved due to the therapeutic efficacy of multi-modality therapy (Raney *et al.*, 1983; Maurer *et al.*, 1988).

Studies of the DNA content by flow cytometry have indicated a correlation between the DNA ploidy and the biological course and response to therapy in certain paediatric neoplasms (Look *et al.*, 1982; Look *et al.*, 1984; Gansler *et al.*, 1986; Schmidt *et al.*, 1986). Similar studies done with rhabdomyosarcoma are few in number. In these studies, investigators have suggested that DNA ploidy analysis may provide a reliable biological parameter in evaluating these neoplasms (Boyle *et al.*, 1988; Molenaar *et al.*, 1988; Shapiro *et al.*, 1991). This has been challenged by Kowal-Vern *et al.* (1990) who found no correlation between DNA content and prognosis.

Studies of rhabdomyosarcoma in adults in general, and of the head and neck in particular, are sparse. In Lloyd *et al.* (1983)'s study only 7.0 per cent of 54 sarcomas were in the head and neck. The paucity of information regarding the natural history and the response to therapy of adult head and neck rhabdomyosarcoma, and the lack of unanimity regarding the role and extent of the disease, histological classification and tumour location in assessing these neoplasms are factors that have hampered efforts to assess the biological behaviour of these neoplasms in a non-paediatric population.

We have analyzed, for the first time, the DNA content in a cohort of adult patients with head and neck rhabdomyosarcomas in an effort to determine its role in the clinicopathological assessment of these neoplasms. The demographic data and the clinicopathological features in our study are similar to those of previously published series (Lloyd *et al.*, 1983; Prestidge and Donaldson, 1989; Nakhleh *et al.*, 1991).

An aneuploid DNA content was manifested in the majority of the neoplasms (97.4 per cent) irrespective of their histological pattern, clinical stage, location or size. Only one neoplasm had a diploid DNA content. The patient had an alveolar histological subtype, stage II disease and died because of the neoplasm within six months of the diagnosis. The preponderance of an aneuploid DNA content found in our patients is similar to the findings in studies of paediatric rhabdomyosarcoma (Boyle *et al.*, 1988; Molenaar *et al.*, 1988; Shapiro *et al.*, 1991). Our data, indicate that, in addition to the preponderance of DNA aneuploidy, adult head and neck rhabdomyosarcoma also manifests a high frequency of multiploidy. Five (23 per cent) tumours in this series showed more than one abnormal stemline. Other investigators have also observed a similar heterogeneity in paediatric rhabdomyosarcomas (Molenaar *et al.*, 1988; Shapiro *et al.*, 1991). These findings presumably represent marked chromosomal abnormalities and instabilities that presage an abnormal clonal evolution which influences tumour progression and response to therapy.

It is of interest, however, that the two surviving patients in this series had stage I neoplasms with an alveolar subtype that were located in non-parameningeal sites. These findings indicate that patients with low stage, non-parameningeal neoplasms pursue a less aggressive clinical course. This observation is in agreement with some previous paediatric (Sutow *et al.*, 1982; Pizzo and Triche, 1987) and adult head and neck rhabdomyosarcoma studies (Lloyd *et al.*, 1983). It should also be realized, however, that a patient with similar characteristics in our series pursued an aggressive course.

Our data are in accord with those of Kowal-Vern *et al.*

(1990) on the lack of correlation between DNA content and the subsequent clinical course in these neoplasms. These results, however, differ from those of Kowal-Vern *et al.* (1990) and Shapiro *et al.* (1991) in the frequency of ploidy patterns and their correlation with the histological subtype in these neoplasms. Contrary to their findings, we found a low incidence of DNA diploidy, and a lack of correlation between the DNA ploidy pattern and the histological sub-classification.

Our results are in agreement with some, (Lloyd *et al.*, 1983; Nakleh *et al.*, 1991) but not with others, (Hays *et al.*, 1983) regarding the absence of correlation between the histological subtype and the biological behavior of these neoplasms. The lack of a consensus between studies may possibly be due to a non-uniform pattern in some rhabdomyosarcomas, and the lack of universal and reproducible criteria for histological classification.

The unpredictability of any parameter is evident by noting that one of our patients (case no. 2) had a small, stage I, non-parameningeal rhabdomyosarcoma which exhibited a decidedly aggressive biological course.

In our small series, we also found no correlation between DNA ploidy pattern and the response to therapy. This is contrary to the findings reported by Molenaar *et al.* (1988) in paediatric patients. The differences may be due to pathophysiological factors such as a higher tolerance of pediatric patients to chemotherapeutic agents.

Our study indicates that adult rhabdomyosarcomas of the head and neck are proponderantly DNA aneuploid, and biologically aggressive neoplasms. We found no correlation between the histological subtype, tumour site, tumour stage, and the biological behaviour and DNA ploidy pattern. The failure of current parameters to accurately stratify patients with rhabdomyosarcoma for treatment modalities indicates a need for better prognostic markers. Further studies to identify the mechanism of aneuploidy and the underlying chromosomal abnormalities may lead to the identification of oncogenes and/or suppressor genes that could be responsible for the varying biological behaviour in adult rhabdomyosarcomas (Seidal *et al.*, 1982; Potluri and Gilbert, 1985; Trent *et al.*, 1985; Scrable *et al.*, 1987; Wang-Wuu *et al.*, 1988; Kumar *et al.*, 1990; Barr *et al.*, 1991; Rodriguez *et al.*, 1991).

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