

## Laryngeal embryonal rhabdomyosarcoma in an adult. A case report and review of the literature

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*Rhabdomyosarcoma (RMS) arising from the larynx in an adult is extremely rare. We hereby report the case of a 20-year-old man with vocal cord embryonal rhabdomyosarcoma. The only clinical symptom was hoarseness. Conservative treatment consisted of concomitant radiochemotherapy with neoadjuvant (vincristine, actinomycin D, cyclophosphamide) and adjuvant multiagent chemotherapy. Conventionally fractionated external beam radiotherapy was given to the larynx in a total dose of 70 Gy. Complete regression of the RMS was obtained. No functional impairment and no evidence of disease was observed during 30 months of follow up. A review of the literature is presented.*

### Mięsak zarodkowy z mięśni poprzecznie prążkowanych krtani u dorosłych. Opis przypadku i przegląd literatury

*Mięsaki z mięśni poprzecznie prążkowanych są nadzwyczaj rzadkimi nowotworami krtani u dorosłych. Przedstawiono przegląd literatury oraz opisano przypadek 20-letniego chorego z rozpoznaniem postaci zarodkowej mięsaka z mięśni poprzecznie prążkowanych, który rozwinął się w obrębie struny głosowej. Jedynym objawem klinicznym była chrypka. Pacjent leczony był zachowawczo – zastosowano neoadjuwantową chemioterapię, skojarzoną jednoczasową radiochemioterapię a następnie uzupełniające leczenie chemiczne. Uzyskano całkowitą regresję nowotworu. W trakcie trzydziestomiesięcznej obserwacji nie stwierdzono progresji nowotworu.*

**Słowa kluczowe:** mięsak zarodkowy, krtień, radioterapia, chemioterapia, głowa i szyja

**Key words:** embryonal rhabdomyosarcoma, larynx, radiotherapy, chemotherapy, head and neck cancer

### Introduction

Rhabdomyosarcoma (RMS) is an aggressive malignant tumor arising from cells of embryonal mesenchymal origin with a potential for differentiating into skeletal striated muscles. RMS can occur in any site of the body where mesenchymal cells are present.

Rhabdomyosarcomas are divided into five pathological types: embryonal, botryoid, spindle cell, alveolar and pleomorphic [1]. Embryonal type of RMS, usually observed in children, is a chemo- and radiosensitive neoplasm. Chemotherapy and irradiation is the recommended treatment of choice. Other types of RMS are treated by surgery.

Rhabdomyosarcoma, especially its embryonal type, is the most common soft tissue sarcoma in children and comprises some 37%-40% of all childhood malignancies

in the head and neck region [2, 3]. RMS is rarely observed in adults, in whom alveolar and pleomorphic types are more common. Adult RMS accounts for less than 10% of all soft tissue sarcomas of the head and neck and less than 1% of malignant tumors in this region [2, 4, 5]. Most frequent localizations of RMS in the head and neck region are the orbits and the parameningeal region [6]. Sarcomas of the larynx in adults are very rare; less than 1-2% of all soft tissue malignancies in the head and neck region [5, 7]. Cady et al. reported 2500 laryngeal tumors and found only 31 sarcomas [8]. In Gorenstein's study only 3 among 3100 tumors of the larynx were rhabdomyosarcomas [7]. Embryonal rhabdomyosarcoma of the larynx in adults is extremely rare. We have found only 9 cases of this tumor reported in literature. Although in the past patients with laryngeal rhabdomyosarcoma usually underwent mutilating surgical procedures (laryngectomy), current data suggest that the embryonal type, in comparison to alveolar and pleomorphic types, could be successfully treated with a combination of radiation and multi-drug chemotherapy [2, 9-13].

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## Case report

In October 1997 a 20 year old man was admitted to the Maria Skłodowska-Curie Memorial Cancer Center (MSCMCC) with the diagnosis of laryngeal rhabdomyosarcoma. The only subjective symptom of disease was a one-year history of gradually intensified hoarseness. The patient had never smoked.

Indirect laryngoscopy performed in another hospital showed a sessile haemorrhagic polypus in the 2/3 anterior part of the right vocal cord. True glottis was wide and vocal cords were movable. Physical examination showed no enlargement of neck lymph nodes. Distant metastases were excluded. In September 1997, microlaryngoscopy and polypectomy was performed. Intensive bleeding was observed during this procedure. Postoperative recovery was uneventful. Sixteen days following surgery indirect laryngoscopy showed rapid tumor progression.

A pale pathologic mass with an uneven surface arising from the central part of the right vocal cord was found and the patient was referred to the department of Head and Neck Cancer of the MSCMCC in Warsaw.

Histopathology slides from previous surgery stained with hematoxylin and eosin (HE) and periodic acid-Schiff (PAS) were reviewed. For immunohistochemical studies, sections were examined by the avidin-biotin-peroxidase complex (ABC) technique, using the following antibodies: vimentin (V 9, dilution 1/2, Sigma) and desmin (D 33, dilution 1/50, Dako). Appropriate negative controls were employed throughout. A polypoid sessile mass 5 mm in diameter was evident microscopically, at low power. It was covered by squamous, partly exulcerated epithelium. The lesion showed a varying degree of cellularity with a predominance of hypercellular areas. Hypocellular myxoid areas were seen occasionally, especially just below the epithelium. The tumour showed, for the most part, features corresponding in morphological appearance to muscle in the fifth to eighth week of normal rhabdomyogenesis. It consisted of small and larger round and oval cells. The cytoplasm of larger cells was prominent, eosinophilic and eccentric. It contained granular

material or delicate fibrillary material arranged concentrically near to or around the nuclei. Spindle type components with large eosinophilic cytoplasm in a strap, ribbon, racket shape (morphological equivalent of the ninth to five-teenth weeks of rhabdomyogenesis) were visible focally. The nuclei of these neoplastic cells varied slightly in size and shape; they were moderately hyperchromatic and had one or two, usually small, but sometimes prominent, nucleoli. Microscopically, sporadic areas of small, spindle shaped undifferentiated cells with hyperchromatic nuclei and scanty cytoplasm were revealed in the myxoid fields. Mitotic activity was sporadic and no necrosis was found.

Glycogen was demonstrable in larger polygonal and spindle shaped cells, which were regarded as well differentiated rhabdomyoblasts. A very strong positive reaction for vimentin and desmin was revealed these cells. Small undifferentiated cells were also desmin positive. Neoplastic cells were arranged haphazardly in a scanty extracellular matrix with a small haemorrhagic and granulate reaction.

The final pathology diagnosis was: embryonal rhabdomyosarcoma (report No: P/K 29758; examiner: D. Pietrow, M.D.)

The patient was referred for combined modality treatment with chemotherapy and irradiation. Initially, three courses of neoadjuvant chemotherapy (vincristine 2 mg iv – day 1; actinomycine D 1 mg iv – day 1,2; cyclophosphamide 1200 mg iv – day 1,2 repeated every 3 weeks) were administered over a period of 2 months. Chemotherapy tolerance was acceptable and partial regression of the tumor was observed.

Between January and March 1998 concomitant radiation and chemotherapy was performed. Conventionally fractionated irradiation with Co60 external beams was given to the larynx with a wide margin, to a total dose of 70 Gy during 7 weeks of treatment. Simultaneously the patient received 3 courses of chemotherapy (vincristine, actinomycine D and cyclophosphamide). Tolerance of this part of treatment was moderate. G3 acute skin and mucosal reactions were observed. According to

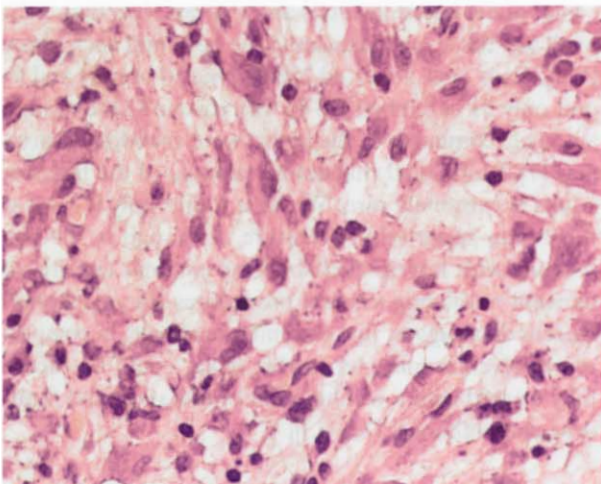


Figure 1. RMS laryngis (original magnification 400x)

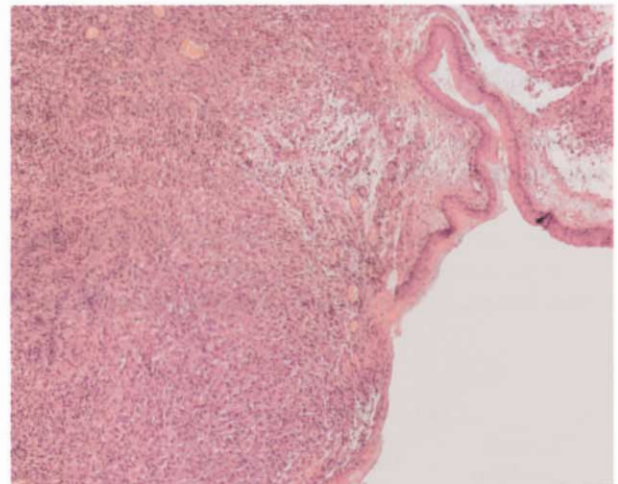


Figure 2. RMS laryngis (original magnification 100x)

the RTOG/EORTC scale, however not influencing treatment protocol. The patient completed radiochemotherapy with complete regression of the tumor. After that he was referred for adjuvant chemotherapy (vincristine 1mg iv – day 1; actinomycine D 0,5mg iv – day 1,2; cyclophosphamide 300 mg iv – day 1,2, repeated every 3 weeks). He received a total of 10 courses. Vincristine doses were reduced to 0.5 mg/day during the two last courses, because of a transient increase in bilirubin level. No other serious adverse effects were observed. The treatment was completed in October 1998. Thirty months later the patient remains free from local recurrence and distant metastases. No functional impairment of the larynx is being observed.

## Discussion

The first case of laryngeal rhabdomyosarcoma in adults was described by Glick in 1944. Only 28 cases of RMS were reported in this localization before 1984 [12]. Diehn et al. found only 6 adult patients with an embryonal subtype of RMS of the larynx [12]. In this analysis, based on 20 cases of rhabdomyosarcoma of the larynx in children and adults, this histological subtype was the most common in adults (6/10 cases). We have found only 9 documented cases of laryngeal embryonal RMS in adults, diagnosed between 1952 and 1998 (Table I). All patients were male. Their age ranged between 20 and 63 years. Four of them underwent laryngectomy as sole treatment (3 total and 1 subtotal). Two other patients were referred for radiation therapy alone. Two patients were treated with surgery (partial laryngectomy and total laryngectomy with neck dissection) followed by radiotherapy. Combined radio- and chemotherapy was carried out only in our patient. One patient was observed without any treatment. Three patients died within 1 year after treatment and one in the second year of observation. In one case no follow-up

was conducted and two other patients died due to postoperative complications. Three patients were alive at 12, 17 and 24 months after treatment.

Embryonal subtype of RMS appears more often in children and adolescents, and is commonly diagnosed in the head and neck region [7, 15-17]. This subtype has better prognosis than alveolar [3]. RMS is a systemic disease and about 10 to 20% patients have clinically detectable secondaries at the moment of diagnosis [18, 19]. Distant metastases are a common cause of failure in head and neck localisation (except for the orbit and parameningeal site) [19, 20]. Cervical lymph node involvement is observed in 3-25% of patients [2, 21]. Distant metastases usually occur in lungs, central nervous system, bones and bone marrow, liver and soft tissues [21, 22]. Localisation, size and stage of tumor and histology type are prognostic factors which may influence local control as well as survival. According to Intergroup Rhabdomyosarcoma Study (IRS) a pretreatment staging system, head and neck region is included into favourable sites [21]. All non-parameningeal sites regardless of tumor size and lymph node involvement are included into stage I°. The best results are observed in patients with orbital localisation. Parameningeal rhabdomyosarcomas have worse prognosis than other head and neck RMS [19]. Neck localisation has a higher incidence of recurrence [23]. Lymph node metastases are a poor prognostic factor. Age is an important prognostic factor; younger patients have better outcome than older [24].

Classification of RMS (ICR) based on results of IRS-II data, divides histological types into prognostic groups. Patients with embryonal rhabdomyosarcoma have an intermediate prognosis [21]. Eighty percent of recurrences are observed within 2 years of treatment [19], and 95% within 3 years [20]. Progression during primary treatment, distant metastases or local recurrence dramatically decrease median survival [17, 19, 25].

Table I. Laryngeal embryonal rhabdomyosarcoma in adults

No	Autor/ year of diagnosis	Age/sex	Treatment	Follow-up
1.	Giraud / 1952 [14]	55 / M	Total laryngectomy, Neck dissection (N+), radiotherapy	D 10 months
2.	Diehn / 1954 [12]	24 / M	Radiotherapy	D < 8 months
3.	Pearsons / 1956 [14]	54 / M	Total laryngectomy	Died post op.
4.	Rodriguez, Ziskind / 1970 [7]	57 / M	Total laryngectomy	No follow-up
5.	Diehn / 1973 [12]	23 / M	Radiotherapy	D 2 years
6.	Rottenburg / 1975 [15]	63 / M	Total laryngectomy	Died post op.
7.	Diehn / 1976 [12]	21 / M	None	D 1 year
8.	Antonova, Dormak / 1978 [15]	55 / M	Subtotal laryngectomy	NED 12 months
9.	Iwsawa / 1978 [15]	25 / M	Radiotherapy, Subtotal laryngectomy	NED 17 months
10.	Rolski, Kawecki, Pietrow, Kiprian, Falkowski /1998, present case	20 / M	Radiotherapy, Chemotherapy	NED 30 months

D-died of disease, NED- no evidence of disease.

Laryngeal rhabdomyosarcoma is more often observed in males [7]. Despite a usually more advanced stage, laryngeal RMS seems to be less aggressive than in other sites in the head and neck region [7]. Tumors of the larynx have a better outcome than those arising from the neck.

Before the 60's patients with RMS were treated only with surgery, resulting in loss of organ functions and cosmetic deformations. However, results of such treatment were unsatisfactory, with a high percentage of local failures and poor long term survival [2, 15, 21]. In general, survival ranged from 10% to 30% [12]. Introduction of radiotherapy and multiagent chemotherapy to the treatment procedures improved the outcome [15, 17].

In the IRS-I trial with VAC (vincristine, actinomycin, cyclophosphamide) and radiotherapy, 2-year survival in stage I to III were 96% to 85% [12], and 80% to 52% of patients were alive 5 years after treatment [25]. No benefit from adding anthracyclines to VAC protocol in stage III was observed [25]. As a result of better prognosis due to combined treatment the role of surgery has been reduced. Embryonal rhabdomyosarcoma cells are very sensitive to chemotherapy. Single agent activity demonstrate vincristine (VCR) (59% of response), actinomycin D (Act-D) (24%), cyclophosphamide (CTX) (54%), cisplatin (15-21%), dacarbazine (11%), mitomycin C (36%), ifosfamide (86%) and etoposide (15-21%) [21]. Current treatment protocols are based on multiagent chemotherapy with VCR, ACT-D, CTX, ADM and radiation therapy [21].

Many studies have demonstrated that surgery is not necessary in the treatment of laryngeal RMS in children. Conservative procedures consisting of radio- and chemotherapy allow to avoid the loss of organ function [9, 13, 26]. According to IRS-IV data the most promising results were achieved in patients with stage I embryonal tumors localized in the head and neck region, who had undergone biopsy or incomplete resection. The 3-year relapse-free survival increased from 53% in IRS-III to 90% in IRS-IV. More intensive schedules allow to diminish the role of surgery to biopsy or resection without cosmetic or functional damages [13]. Combined radiation and chemotherapy could be effective even in patients with lymph node involvement, but neck dissection and postoperative radiotherapy might be indicated in cases with multiple nodal metastases [10].

VAC seems to be the most promising regimen for patients with unresected tumor in the head and neck region. Addition of ADM increases toxicity without benefit measured in prolonged survival. Radiotherapy can assure local control in gross as well as in microscopic disease [18]. The IRS-I study revealed that local control rate depended on a dose of radiotherapy [25]. Patients with embryonal subtype who had received radiotherapy had better relapse-free survival, but no difference in overall survival was observed [17].

Probability of local control in children with macroscopic RMS tumor (after biopsy or partial excision) was higher in patients who received more than 50 Gy (doses ranged from 50 to 72 Gys) [11]. The planning target volu-

me should include region the involved before chemotherapy. Elective nodal irradiation is not necessary [26]. Efficacy of hyperfractionation was evaluated in some recent studies [3].

The modality of treatment (VAC chemotherapy + concurrent radiochemotherapy + adjuvant chemotherapy) used in our patient seems to be one of the most effective in embryonal rhabdomyosarcoma of the head and neck region.

## Conclusions

The review of literature suggests that systemic treatment and radiation therapy allow to achieve good local control and to preserve organ function in patients with embryonal rhabdomyosarcoma of the head and neck region. The results of treatment in the presented case of RMS of the larynx confirm this suggestion.

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