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Full Length Article

Clinical significance of anaplasia in childhood rhabdomyosarcoma

Iman Sidhom [a], Enas El Nadi [b,*], Hala Taha [c], Naglaa Elkinaai [c], Mohamed S. Zaghloul [d], Alaa Younes [e], Rania Labib [f], Mohamed Sabry [f]

[a] Pediatric Oncology Department, Children Cancer Hospital Egypt (CCHE), National Cancer Institute, Cairo University, Egypt
[b] Pediatric Oncology Department, Children Cancer Hospital Egypt (CCHE), BeniSuef University, Egypt
[c] Pathology Department, Children Cancer Hospital Egypt (CCHE), National Cancer Institute, Cairo University, Egypt
[d] Radiotherapy Department, Children Cancer Hospital Egypt (CCHE), National Cancer Institute, Cairo University, Egypt
[e] Surgery Department, Children Cancer Hospital Egypt (CCHE), National Cancer Institute, Cairo University, Egypt
[f] Research Department, Children Cancer Hospital Egypt (CCHE), Egypt

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KEYWORDS

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Abstract *Background:* The presence of anaplastic features has been known to correlate with poor clinical outcome in various pediatric malignancies, including Wilms tumor and medulloblastoma but not in rhabdomyosarcoma.

Aim: Aim was to study the frequency of anaplasia at presentation in childhood rhabdomyosarcoma and its relationship to clinical and pathological characteristics as well as to outcome.

Patients and Methods: Anaplasia was retrospectively assessed in 105 consecutive pediatric rhabdomyosarcoma patients who were registered at the Children's Cancer Hospital in Egypt (CCHE) during the period from July 2007 till the end of May 2010.

Results: Anaplasia was diagnosed in 18 patients (17.1%), focal in 10 (9.5%) and diffuse in 8 (7.6%). The distribution of anaplasia was found to be more common in older patients having age $\geqslant$ 10 years. Also it was more likely to occur in the high risk group and in tumors with unfavorable histology (alveolar subtype), and stage IV. The 3-year failure free survival rates for patients with and without anaplasia were 27.8 ± 10.6% and 53.4 ± 5.8%, respectively (p = 0.014) and the 3-year overall survival rates were 35.3 ± 11.6% and 61 ± 6%, respectively (p = 0.019).

Conclusions: The frequency of anaplasia in pediatric patients with rhabdomyosarcoma in our study was 17.1%. The presence of anaplasia had statistically significant worse clinical outcome.

Introduction

Rhabdomyosarcoma (RMS) is the fourth most common pediatric solid tumor with increasing incidence, predominantly

* Corresponding author at: 1 SeketElEmam, SayedaZeinab, Cairo, Egypt. Tel.: +20 1222786478.
E-mail address: elnadienas@gmail.com (E. El Nadi).

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affecting young children. Multimodal treatment has improved survival significantly during the last decades to approximately 70% [1]. The intensity of treatment depends on the estimated relapse risk, thus treatment is risk adapted. Extent of disease, primary tumor site, clinical group and histology have been associated consistently with prognosis [2] and thus have proven useful for the development of risk-based therapy. Although the majority of patients achieve a complete remission (CR) with primary therapy, a substantial number still experience recurrences with poor prognosis [3,4]. More accurate estimation of prognosis is needed to improve patient stratification and permit further treatment tailoring according to relapse risk.

Rhabdomyosarcoma can be divided into several histologic subsets: embryonal rhabdomyosarcoma, which has embryonal, botryoid, and spindle cell subtypes; alveolar rhabdomyosarcoma; and pleomorphic rhabdomyosarcoma.

Pleomorphic rhabdomyosarcoma occurs predominantly in adults aged 30 to 50 years and is rarely seen in children [4]. In adults, pleomorphic rhabdomyosarcoma is associated with a worse prognosis. In children, the term *anaplasia* is preferred.

Anaplasia is rare in childhood rhabdomyosarcoma and has not been included in the International Classification of Rhabdomyosarcoma (ICR). A review of the Soft Tissue Sarcoma Committee of the Children's Oncology Group (COG) suggests that anaplasia might be more common than previously reported and may impact clinical outcome [5].

The degree of anaplasia was further defined not just by relative quantity but also apparent clonal expansion of the anaplastic nuclei in the tumor. Type I tumors as defined by Kodet included anaplastic cells loosely scattered among non-anaplastic cells (so called focal anaplasia), and type II tumors included those with anaplastic cells that were aggregated in clusters or formed continuous sheets. Despite the suggestion that anaplasia could significantly affect outcome, its relative rarity and lack of reproducibility on multi-reviewer studies precluded incorporation of this feature as a morphologic criteria for assessment in the International Classification of Rhabdomyosarcoma [5].

A better understanding of biologic differences and new, active agents is needed to improve outcome of patients with unfavorable features at presentation [10].

The aim of this work was to study the frequency of anaplasia at presentation in childhood rhabdomyosarcoma and its relationship to clinical and pathological characteristics as well as to outcome.

Patients and methods

One-hundred and five consecutive pediatric patients with newly diagnosed rhabdomyosarcoma who were registered at the Children's Cancer Hospital in Egypt (CCHE) during the period from July 2007 till end of May 2010 were included in this study. Their ages ranged from 2 months to 17.7 years. They included 70 males and 35 females.

All pathological materials were reviewed blindly by two pathologists for the presence of anaplasia. Cases were categorized according to the International classification of Childhood Sarcomas [6].

Anaplasia was defined as the presence of multipolar polyploid mitotic figures with marked nuclear enlargement and hyperchromasia (at least 3 times the size of neighboring nuclei). Anaplastic cells present in one or a few sharply localized regions within the primary tumor were categorized as focal anaplasia, while those that were aggregated in clusters or formed continuous sheets were considered as diffuse anaplasia [7].

The presence or absence of anaplasia (diffuse or focal) was correlated with clinical and pathological variables including age, sex, primary tumor site, histologic subtype, IRS clinical group, stage, tumor size, tumor invasiveness and nodal status as well as to clinical outcome.

Staging and classifications

Tumors were classified according to the Intergroup Rhabdomyosarcoma Study (IRS) pretreatment TNM staging [8] and grouping system [9]. Imaging and surgery determined the extent of disease for assignment of IRS Stage and Group, respectively. Tumors were categorized according to sites of origin into favorable sites (orbit, non-parameningeal head and neck, genitourinary other than bladder and prostate) or unfavorable (extremity, bladder, prostate, parameningeal sites, retroperitoneum, trunk, other). Histology was determined as embryonal (including spindle cell and botryoid subtypes), and non-embryonal histology that included alveolar subtype and undifferentiated.

Therapy

Patients were treated with risk adapted combined modality treatment including surgery, multiagent chemotherapy and/or radiotherapy.

Therapy was assigned based on the IRSG rhabdomyosarcoma risk group classification [10,11]. Patients were classified according to the stage, clinical group and histological subtype into:

a. **Low risk group**: Included patients with embryonal RMS or botryoid who had:
   - Non-metastatic tumors arising in favorable sites (stage1), clinical group I, II, or III.
   - Non-metastatic tumors in unfavorable sites (stage 2 or 3) that are grossly resected with or without microscopic residual (clinical group I or II).
b. **Intermediate risk group**: Included patients with:
   - Embryonal RMS or botryoid who had stage 2 or 3 and clinical group III.
   - Alveolar RMS who had stage 1, 2, or 3 and clinical group I, II, or III.
   - Non metastatic Parameningeal primary site regardless of the histology who had clinical group I, II, or III.
c. **High risk group**: Included all metastatic patients with stage 4.

Chemotherapy

Treatment protocol is summarized in Table 1.

Local therapy

A delayed surgery if possible was performed for patients with clinical group III disease on week 12. No radiotherapy was