Ewing's sarcoma family tumors in the western region of Saudi Arabia

A pathological experience from 2 tertiary medical centers

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ABSTRACT

الأهداف: مراجعة نمط حدوث ساركومةُ يُوِينْغ من خلال مراجعة الحالات المسجلة بمستشفيين بالمنطقة الغَربية بالمملكة العربية السعودية.

الطريقة: أُجريت هذه الدراسة الاسترجاعية بمراجعة تقارير التحليل النسيجي بمختبري علم الأمراض بمستشفى جامعة الملك عبد العزيز خلال الفترة من مارس 1995 إلى نوفمبر 2011، و مستشفى الملك فيصل التخصصي خلال الفترة من ابريل 2003 إلى ديسمبر 2010. لقد تمت مراجعة البيانات بتقارير المرضى مثل السن والجنس وخصائص الورم.

النتائج: أشارت نتائج الدراسة إلى وجود 69 حالة ساركومةُ يُوِينْغ في هذه الفترة بمعدل عمر يتراوح ما بين 62–3 عاماً (متوسط 22 عام). ولقد كانت نسبة حدوث الورم بالذكور أعلى من نسبة الإناث، ونسبة حدوث الورم بالهيكل العظمي 28.9% وهي أقل من نسبته بالأنسجة الرخوة التي كانت 71.1%. وكان عظم الحوض الأعلى حدوثاً بالهيكل العظمي. بالإضافة إلى ذلك فقد كانت نسبة الحدوث في العظام الطويلة أقل، واحتلت منطقة الرأس والرقبة النسبة الأعلى في الأنسجة الرخوة، تلتها منطقة الطرف السفلي.

خاتمة: لقد قمنا في هذه الدراسة بمراجعة عدد كبير من ساركومةُ يُوِينْغ بالمنطقة الغربية بالمملكة العربية السعودية، حيث أوضحت تشابه الخصائص الإكلينيكية الباثولوجية مع الدراسات المسجلة من بلدان أخرى، ولكن الدراسة أثبتت ارتفاع حدوث الورم بالأنسجة الرخوة أكثر من الهيكل العظمي مع حدوث الورم بمنطقة الرأس والرقبة بنسبة أعلى. يتطلب هذا الورم المزيد من الأبحاث على عدد أكبر من الحالات من مناطق مختلفة بالمملكة العربية السعودية لتحديد نمط المرض والتغيرات الجينية التي قد تكون مميزة للمرضى السعوديين ومدى تأثير ذلك في التنبؤ بطرق العلاج.

Objectives: To review the pattern of Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET) in 2 medical centers in the western region of Saudi Arabia.

Methods: We retrospectively analyzed the pathological data of patients diagnosed with ES/PNET in 2 tertiary medical centers in the western region of Saudi Arabia (King Abdulaziz University Hospital, [March 1995 to November 2011], and King Faisal Specialized Hospital [April 2003 to 12 December 2010]). Age, gender, and site of tumors were analyzed.

Results: Sixty-nine cases were diagnosed as ES/PNET. The age range was 3-62 years (mean 22 years). Male cases were more than the female. Approximately 28.9% of cases presented within the skeleton, and 71.1% cases were presented as a soft tissue disease. Bone affection was higher in the iliac bone. Long bones were affected at a lower frequency. Soft tissue affection showed a higher incidence in the head and neck region followed by the lower limb.

Conclusions: The current study represents a review of a large number of Ewing's sarcoma family of tumors in western Saudi Arabia. Cases showed clinicopathological features comparable to those reported from other locations worldwide apart from relatively higher soft tissue affection than skeletal affection and a higher incidence of head and neck involvement by soft tissue ES/PNET. Further, multicenter studies (epidemiological and genetic) are recommended to obtain profiling of the disease and effect on outcome and therapy.

Saudi Med J 2012; Vol. 33 (4): 418-422

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Received 22nd November 2011. Accepted 27th February 2012.

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Ewing's sarcoma family of tumors (EFT) (Ewing's sarcoma [ES] and primitive neuroectodermal tumor [PENT]) is uncommon tumors and arise in mesenchymal tissues.[1,2] This family of tumors has a guarded prognosis.[3] Ewing's sarcoma accounts for approximately 10% of malignant bone tumors.[4] They are the second most common malignant bone neoplasm after osteosarcoma[1] and the second most common bone tumor in children and adolescents.[5] Ewing's sarcoma family belongs to a group of tumors histologically named the small round blue cell tumors of the bone. Ewing's sarcoma family of tumors includes classical Ewing sarcoma of bone, extraskeletal Ewing's sarcoma, and peripheral primitive neuroectodermal tumor. This group includes Ewing's sarcoma shows a strong membrane immunostaining staining for CD99, with an incidence primarily in Caucasians.[6,7] Ewing's sarcoma and PNET exhibit similar translocations and so are considered to a histological spectrum of EFT.[8] The clinical presentation and prognosis of many malignancies differ according to the ethnic origin and race.[9] However, the effect of race and ethnicity on ES/PNET has not been demonstrated well. Patient and tumor characteristics in Ewing's sarcoma differ by race and ethnicity. The objective of this study is to retrospectively review the clinicopathological pattern of EFT in 2 medical centers in western Saudi Arabia (King Abdulaziz University Hospital and King Faisal Specialized Hospital) over a decade.

Methods. We retrospectively reviewed patients diagnosed with ES/PNET in 2 tertiary medical centers in Jeddah (King Abdulaziz University Hospital from March 1995 to November 2011 and King Faisal Specialized Hospital and Research Center from April 2003 to December 2010). The study was in accordance with the Bioethical and Research Committee of Faculty of Medicine, King Abdulaziz University, Saudi Arabia and according to the ethical guidelines of the 1975 Declaration of Helsinki.

Patients' histological materials were retrieved from the archive; age, gender, and tumor were analyzed. The histopathological slides of each case were re-examined. Hematoxylin and eosin stained slides together with periodic acid schiff (PAS) stain, and immunohistochemistry material including CD99 was reviewed. The pathological material was reviewed by 2 pathologists. Each diagnosis was established based on the presence of small round cells, with membranous staining for CD99 and the absence of histological or immunohistochemical features of rhabdomyosarcoma, lymphoma, or neuroblastoma.

Chi square test was used to compare the distribution of variables. Data analysis was carried out using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), Version 16. A p-value <0.05 was considered significant and 95% confidence intervals are expressed as a 2-sided range.

Results. A total number of 69 cases were diagnosed as ES/PNET. Of which 37 (53.6%) were male and 32 (46.4%] were female (p=0.628, CI=0.050-0.950). The age range was 3-62 years (mean: 22 years). The highest incidence located in the second decade followed by third decade with male predominance in each (**Table 1**). In 20 cases (28.9%), the tumors were presented within the skeleton (skeletal Ewing's sarcoma) and 49 cases (71.1%) were presented as a soft tissue disease (extraskeletal Ewing's sarcoma) (p=0.001 CI=0.000-0.950). Age incidence in relation to site of the lesion are summarized in **Table 2**. Iliac bone showed the highest frequency of affection within skeleton (**Table 3**) (p=0.001, CI=0.000-

Table 1 - Age distribution of 69 cases diagnosed with Ewing's sarcoma and primitive neuroectodermal tumor in 2 tertiary medical centers in Jeddah, Saudi Arabia.

Age group	Male/Female	n	(%)
<10 years	3/2	5	(7.2)
10-19 years	19/11	30	(43.5)
20-29 years	12/11	23	(33.3)
30-39 years	2/4	6	(8.7)
40-49 years	3 female	3	(4.3)
50-59 years	1 female	1	(1.5)
≥60 years	1 male	1	(1.5)

Table 2 - Age distribution in relation to site of the lesion (N=69).

Site	Mean±SD	Male/Female
Soft tissue	22.25 ± 10.505	23/26
Head and neck	20.8 ± 9.874	5/6
Lower limb	20.8 ± 8.768	4/6
Pelvis	29.375 ± 14.222	3/5
Spinal cord	21.0 ± 6.271	3/1
Upper limb	23.5 ± 13.126	2/2
Chest wall	15.25 ± 8.995	1/2
Lung	24.0 ± 15.556	1/2
Liver	17.0 ± 0.0	1/1
Pleural	36.0 ± 0.0	1/0
Mediastinal	25.0 ± 0.0	0/1
Abdomen	19.0 ± 0.0	1/0
Back	22.0 ± 0.0	1/0
Skeletal	22.94 ± 12.359	13/7
Iliac bone	17.858 ± 4.375	5/2
Scapula	20.5 ± 6.363	21/1
Mandible	16.0 ± 4.242	1/1
Tibia	25.5 ± 0.707	1/1
Vertebra	32.0 ± 18.384	1/1
Femur	22.0 ± 0.0	1/0
Fibula	22.0 ± 0.0	1/0
Knee	270 ± 0.0	0/1
Ischium	62.0 ± 0.0	1/0
Humerus	24.0 ± 0.0	1/0

0.950) followed by scapula and mandible. Long bones were affected in a lower frequency. Soft tissue affection showed a higher frequency of incidence in the head and neck region followed by lower limb (**Table 4**) (p=0.827, CI=0.050-1.000). Histologically these tumors are composed of sheets of small uniform primitive cells with little cytoplasmic rim together with glycogen content (**Figures 1a-1d**). Tumor cells show strong diffuse membranous immunostaining for CD99 which is a characteristic feature for this group of malignancy (**Figure 1b**).

Table 3 - Site distribution of skeletal Ewing's sarcoma and primitive neuroectodermal tumor in tertiary medical centers in Jeddah, Saudi Arabia (n=20).

Site	n	(%)
Iliac bone	7	(35)
Scapula	2	(10)
Mandible	2	(10)
Tibia	2	(10)
Vertebra	2	(10)
Femur	1	(5)
Fibula	1	(5)
Knee	1	(5)
Ischium	1	(5)
Humerus	1	(5)

ES/PNET - Ewing's sarcoma/primitive neuroectodermal tumor

Table 4 - Site distribution of soft tissue Ewing's sarcoma and primitive neuroectodermal tumor in tertiary medical centers in Jeddah, Saudi Arabia (n=49).

Site	n	(%)
Head and neck	11	(22.4)
Lower limb	10	(20.4)
Pelvis	8	(16.3)
Spinal cord	4	(8.2)
Upper limb	4	(8.2)
Chest wall	3	(6.1)
Lung	3	(6.1)
Liver	2	(4.1)
Pleural	1	(2.0)
Mediastinal	1	(2.0)
Abdomen	1	(2.0)
Back	1	(2.0)

ES/PNET - Ewing's sarcoma/primitive neuroectodermal tumor

Discussion. King Abdulaziz University and King Faisal Specialized Hospitals are 2 large tertiary medical centers in western region of Saudi Arabia. This study represents a series of ES/PNET cases diagnosed at the departments of pathology in these institutions. We retrospectively analyzed the data of patients. The current study represents the first to report the pattern of ES/PNET in Saudi Arabia. Previous studies from Saudi Arabia represented series of cases of extraskeletal Ewing's sarcoma or Ewing's sarcoma of localized anatomical location.[10-12] In this study, ES/PNET occurred frequently in male than female patients, which is consistent with previous reports.[13] However, Ayadi et al[14] reported that occurrence of ES/PNET was higher in females than male. But the study group was smaller than ours. Ewing's sarcoma is a rare tumor that is most common in children and young adults[15] and 90% of ES/PNET cases occur before the age of 25 years,[6] which is comparable in our study. In this study, soft tissue ES/PNET tumors were higher (71.9%) than skeletal affection (28.9%) (p=0.001). In a study that involved a large-scale registry from 17 populations in

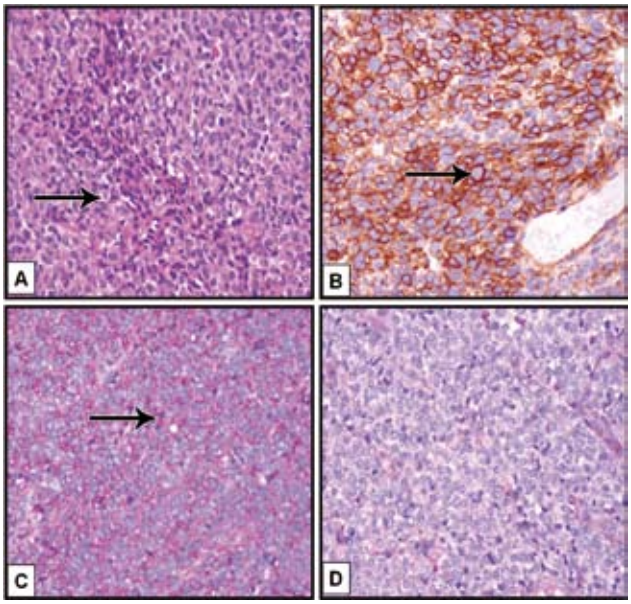

Figure 1 - A panel showing the histological appearance of Ewing's sarcoma in hematoxylin and eosin section. **a)** Tumor cells are small and uniform with round nuclei and scanty cytoplasm. The tumor cells show positive and strong membranous immunostaining for CD99. **b)** Immunohistochemical labelling was carried out with anti-MIC-2 antibody, and diaminobenzidine (DAB) was used as the chromogen and hematoxylin as a counterstain. **c)** Tumor cells contain glycogen and documented by periodic acid schiff (PAS) stain. Intracytoplasmic glycogen was digested by the enzyme diastase and is shown by **d)** PAS-D stain. Original magnification 200x.

the US, Jawad et al,[16] reported a lower incidence of soft tissue ES/PNET tumors than skeletal tumors. Similarly, a report of adult soft tissue, Ewing's sarcoma from Saudi Arabia revealed that skeletal involvement is higher than extraskeletal involvement.[10] This may be explained by their limitation of cases to adulthood occurrence. In our study, the head and neck region had the highest in occurrence of soft tissues (although not statistically significant) ES/PNET followed by lower limbs, while back was the least common site. Martin et al[17] reported the incidence of adult ES/PNET and revealed that head and neck was the least common site. Little is published regarding the site of soft tissue ES/PNET. A far lower percentage of head and neck occurrence was reported by El Weshi et al.[10] The increased number of cases in head and neck cannot be explained; however, a racial and geographical difference may be a contributing factor. This study showed a prediction of skeletal ES/PNET cases to occur in iliac bone (p=0.001), which is similar to the findings of Bhagat et al study,[18] Katchy et al,[19] and Al-Amoudi et al.[20] Other study reported that vertebrae were the most common site.[21] However, others showed that the pelvis was the second most common site involved after the femur.[6,18] Ewing's sarcoma in the pelvis have a worse prognosis than those in extremities[22] because of late diagnosis as lack of specific symptoms, non-specific radiological findings and large size of tumors and gradual growth.[18] Rheumatologists and radiologists should be aware of the disease to provide early diagnosis and improve patients' outcome. In ES, race and ethnic groups affect the tumor characteristics. In black Americans, soft tissue affection is higher when compared to white non-Hispanics. Also, Asian and white Hispanic patients had a different frequency of soft tissue affection from white non-Hispanics.[23] The etiopathogenesis behind these differences is unknown and needs to be investigated.

Although our study is limited to 2 medical centers, it could provide a basis to design a collaborative national study targeting EFT. In addition, more studies are needed to demonstrate the incidence of ES/PNET in Caucasian race and explore the pattern genetic and chromosomal abnormalities.

In conclusion, this study represents a review of a large series of EFT from Saudi Arabia. Cases showed clinico-pathological features comparable to those reported from other locations worldwide apart from relatively higher soft tissue affection than skeletal affection and a higher incidence of head and neck involvement by soft tissue ES/PNET. This is an important finding taking into consideration the significance of the site of involvement in the prognosis and response to therapy. Epidemiological studies are recommended from other provinces in Saudi Arabia to reflect the incidence and the magnitude of the disease in Saudi population. Such multicenter larger studies will allow determination of the genetic profile of the disease in Saudi patients and the relation to disease outcome and response to treatment.

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