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The Spectrum of Mesenchymal Tumors of the Skin

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The Spectrum of Mesenchymal Tumors of the Skin

Cutaneous tumours of mesenchymal origin are relatively uncommon tumors, originating from non-epithelial skin structures and characterized by clinico-pathological heterogeneity. Being classified histologically according to the mature tissue they resemble, these heterogeneous mesenchymal neoplasms show a broad range of differentiation and form the largest group of skin tumors. The aim of the study was to analyze the incidence patterns and clinical peculiarities of cutaneous mesenchymal tumours according to the histologic type. Research trials were conducted in the Institute of Oncology of the Republic of Moldova and included 1121 patients with cutaneous tumors of mesenchymal origin, surgically treated in the period 2004-2008, including 1036 (92.4%) benign tumors and 85 (7.6%) malignant tumors. The most frequent benign tumors were hemangioma (52.4%) and dermatofibroma (33.7%). Kaposi sarcoma was the most common form of cutaneous malignant mesenchymal tumors, accounting for 43.53% of cases. 41.18% of skin tumors of mesenchymal origin were reprezented by dermatofibrosarcoma protuberans, which is a locally aggressive tumor with a high recurrence rate and little metastatic potential. This study demonstrated variation by age, sex and anatomic location in patients with cutaneous sarcomas according to the histologic type.

Key words: cutaneous mesenchymal tumors, Kaposi sarcoma, dermatofibrosarcoma protuberans.

Спектр мезенхимальных опухолей кожи

Мезенхимальные опухоли кожи встречаются редко и возникают из неэпителиальных, мягкотканных компонентов кожи, характеризующиеся клинико-морфологической гетерогенностью. Они составляют разнообразную группу опухолей кожи, согласно морфологической структуре. Данное исследование имело цель определить эпидемиологические и клинико-морфологические особенности опухолей кожи в зависимости от гистологического типа. В работу было включено 1121 пациентов с мезенхимальными опухолями кожи, оперированных в Онкологическом Институте в течение 2004–2008 гг. Из них, 1036 (92,4%) с доброкачественными, 85 (7,6%) с злокачественными опухолями. Согласно исследованию, наиболее частыми доброкачественными опухолями являются дерматофиброма (33,7%) и гемангиома (52,4%). Злокачественные мезенхимальные опухоли представлены саркомой Капоши (43,53%). Выбухающая дерматофибросаркома, которая имеет медленный рост, локально агрессивное течение и склонность к рецидивам, встречается в 41,18% случаев кожных злокачественных мезенхимальных опухолей. По данным исследования существуют вариации по возрасту, полу и анатомической локализации у больных с саркомой кожи в зависимости от гистологического типа опухоли.

Ключевые слова: мезенхимальные опухоли кожи, саркома Капоши, выбухающая дерматофибросаркома.

Introduction

Cutaneous tumours of mesenchymal origin are a heterogeneous group of uncommon tumors, originating from non-epithelial skin structures. Malignant mesenchymal tumors, called sarcomas, are far outnumbered by carcinomas, melanoma and benign mesenchymal neoplasms of skin and subcutis. These heterogeneous mesenchymal neoplasms show a broad range of differentiation and are classified histologically according to the mature tissue they resemble, such as smooth muscle (leiomyosarcoma), endothelium (angiosarcoma), or fibroblast (eg. dermatofibrosarcoma protuberans) [3]. Benign mesenchymal tumors show an incidence of 3.000/1 million people and therefore are about a hundred times more frequent than malignant mesenchymal tumors (incidence of 30/1 million). Cutaneous soft tissue sarcomas represent < 1% of malignant tumors, and little is known regarding their etiology or incidence patterns. Their behaviour varies from indolent to very aggressive, with consequent variation in survival, according to histological type, grade, and sometimes genetic constitution, but the overall 5 year survival is about 65-75%.

Although most tumors arise spontaneously, some risk factors have been identified. Recent reports have linked specific genetic, immunodeficiency, irradiation, and environmental factors as well as viral infection with the development of mesenchymal cutaneous and noncutaneous tumors. The most recent World Health Organization (WHO) classification of soft tissue sarcomas takes into account type-specific cytogenetic and molecular findings in the classification [3]. Some tumors also arise in scars. It is known that the human herpes virus 8 plays a role in the development of Kaposi sarcoma [1,5]. Other risk factors include chronic lymphedema, which increases the incidence of soft tissue sarcomas. Angiosarcoma complicating longstanding lymphoedema especially after radical mastectomy might also be due to local immunosuppression [10]. An association between exposure to herbicides, including dioxin, and sarcomagenesis is controversial and remains unproven. Sarcomas can arise in the field of prior therapeutic irradiation. Following irradiation for carcinoma of the breast, low-grade cutaneous angiosarcomas were noticed after an interval as short as 18 months [8]. Benign and malignant tumours present as usually painless masses, with varying growth rate. Cutaneous lesions form a plaque or elevated nodule that can ulcerate when malignant.

In general, sarcomas in skin or subcutis can be considered part of the group of soft tissue sarcomas and have a more favourable outcome than those located beneath deep fascia. The recent WHO classification of Tumours of Soft Tissue [3] recognizes three behavioural categories:

1. Benign tumours. These rarely recur locally, and those that recur do so in a non-destructive fashion and are usually cured by local excision. Exceptionally rarely, an otherwise (and histologically typical) benign tumour, such as cutaneous fibrous histiocytoma, can metastasize.

2. Intermediate tumours are those that are locally aggressive and/or very occasionally metastasizing, such as dermatofibrosarcoma protuberans. Rarely-metastasizing tumours are generally dermal or subcutaneous tumours which have a low (1-2%) but definite risk of metastasis, most often to regional lymph nodes but occasionally to lung. Examples are recorded for plexiform fibrohistiocytic tumour and angiomatoid fibrous histiocytoma.

3. Malignant tumours infiltrate and recur locally and have an appreciable risk of metastasis (exceeding 20%).

Histologically, malignant soft tissue neoplasms are characterized by nuclear pleomorphism, mitotic activity including abnormal forms, necrosis and vascular invasion. Some benign tumours, however, can show one or more of these features. Examples include nuclear atypia in cutaneous pleomorphic fibroma and atypical benign fibrous histiocytoma (which can also display necrosis), and frequent mitoses in nodular fasciitis.

Grading of tumors is an attempt to predict clinical behaviour based on histological variables. It should be done on material from a primary untreated neoplasm, though change (increase) of grade can be noted in recurrent or metastatic tumor. Of the grading systems that have been developed, those of the French Federation of Cancer Centers Sarcoma Group and the National Cancer Institute (both of which are 3-grade systems) are now the

most commonly used [2,3]. Briefly, tumors are given a score of 1, 2 or 3 depending on the degree of differentiation; 1, 2 or 3 for number of mitoses per 10 hpf (< 10, 11 - 20, or > 20); and 0-2 for amount of necrosis (0, < 50%, > 50%). A total score count of 2 or 3 is classified as grade 1, a score count of 4 or 5 as 2, and a score of 6, 7 or 8 as grade 3.

The staging of sarcomas is based on tumor grade, size, and location. A widely used staging system for soft tissue sarcomas is that of the International Union against Cancer (UICC) (TNM system) and American Joint Commission on Cancer (AJCC). Unlike many other tumours, staging of sarcomas includes histological grading as well as tumour size and depth from surface, regional lymph node involvement and distant metastasis. Cutaneous sarcomas have a lower risk of metastasis than those located deeper; indeed histologically malignant leiomyosarcomas confined to skin are essentially non-metastasizing tumours.

Although some studies have reported the overall epidemiology of soft tissue sarcomas, to our knowledge, no previous study has focused on the population-based epidemiology of cutaneous sarcomas in the Republic of Moldova.

The aim of the study

To conduct a comprehensive analysis of cutaneous tumours of mesenchymal origin, including incidence rates and diagnostical peculiarities according to patient demographic characteristics and histologic type using the most recent criteria of the WHO classification.

Material and methods

Research trials were conducted in the Institute of Oncology of the Republic of Moldova and included 1121 surgically treated patients with cutaneous benign and malignant tumors of mesenchymal origin in the period 2004-2008. The diagnosis was confirmed by histologic examination of slides in all of the cases (100%).

The main part of the cases was represented by benign tumors (92.4%) and only 7.6% - by malignant tumors. The most frequent benign tumors were hemangioma (52.4%) and dermatofibroma (33.7%) (tab. 1). The other cutaneous benign tumors constitued 13.9%.

In the current study, we investigated the epidemiology of soft tissue sarcomas that originated in the skin above the fascia

Table 1

Cutaneous benign tumours of mesenchymal origin diagnosed during 2004 to 2008 by histologic type (number of cases)

Histologic type	2004	2005	2006	2007	2008	Total
Dermatofibroma	70	51	73	84	71	349
Fibroma	8	6	3	4	15	36
Angiofibroma	1	2		5	1	9
Lipoma	1	3	1	2	5	12
Fibrolipoma		5	8	2	4	19
Leiomyoma			1	1	1	3
Angioleiomyoma		1		2	1	4
Capillary hemangioma	39	36	57	58	91	281
Cavernous hemangioma	35	43	34	31	38	181
Capillary-cavernous hemangioma	12	17	13	20	19	81
Neurofibroma	4	11	10	3	10	38
Neurilemmoma					3	3
Neurinoma (shwannoma)	1	1	1	5	4	12
Limfocytoma				1	1	2
Xantoma					3	3
Fibroxantoma			1			1
Juvenile xanthogranuloma					1	1
Abrikosov's tumor					1	1
Total	171	176	202	218	269	1036

Table 2

Cutaneous malignant tumours of mesenchymal origin diagnosed during 2004 to 2008 by histologic type and sex

Histologic type	ICDO-3 Code(s)	Men		Women		All	
		No. of cases	%	No. of cases	%	No. of cases	%
Kaposi sarcoma	9140	24	28.24	13	15.29	37	43.53
Dermatofibrosarcoma protuberans	8832,8833	25	29.41	10	11.76	35	41.18
Leiomyosarcoma	8890-8896	1	1.18	1	1.18	2	2.35
Angiosarcoma	9120,9130,9170	2	2.35	3	3.53	5	5.88
Malignant fibrous histiocytoma	8830	3	3.53	1	1.18	4	4.71
Malignant hemangioendothelioma	9130	1	1.18	1	1.18	2	2.35
Total cutaneous sarcomas		56	65.88	29	34.12	85	100

Table 3

Cutaneous malignant tumours of mesenchymal origin diagnosed during 2004 to 2008 by histologic type and anatomic location

Histologic type	Total no. of cases	Head and neck		Trunk		Upper extremity		Lower extremity		Multisite	
		No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%
Kaposi sarcoma	37	1	2.70	0	0	4	10.81	18	48.65	14	37.84
Dermatofibrosarcoma protuberans	35	10	28.57	14	40.0	6	17.14	5	14.29	0	0
Others	13	2	15.38	3	23.08	2	15.38	6	46.15	0	0

rather than soft tissue sarcomas that arose from the subcutaneous or deeper connective tissue or from specific organs. The incidence data were evaluated for cutaneous soft tissue sarcomas diagnosed from 2004 through 2008 among residents of the Republic of Moldova. Primary site and histologic type for each malignancy were coded according to the third edition of the International Classification of Diseases for Oncology (ICDO-3) [4]. We categorized individual 4-digit histology codes into major histologic groups according to the criteria specified in the latest 2002 WHO classification of soft tissue tumors [3]. The specific morphology codes that were used are shown in tab. 2.

Results and disscusion

In total, 85 cases of cutaneous malignant tumours of mesenchymal origin were diagnosed from 2004 through 2008. The number of cases and percent distribution of these tumors according to histologic type are shown in tab. 2.

Kaposi sarcoma (KS) was the most common form of cutaneous soft tissue sarcomas, accounting for 43.53% of cases. The number of KS cases worldwide in 2002 was estimated at approximately 65,000 [9]. There are 4 main types of KS: classic KS, which typically occurs among elderly Mediterranean men or Ashkenazi Jews; human immunodeficiency virus (HIV)-associated KS; endemic KS, which presents in individuals of Central African countries; and transplantation-related KS [6]. Although classic KS had been reported for over a century before the acquired immunodeficiency syndrome (AIDS) epidemic, it was rare, and its etiology was unknown [1, 6]. With the increase in KS cases, all 4 types of KS have been associated with human herpes virus 8 (HHV-8) [1, 6]. Regardless of the type of KS, the most common site is the skin.

Other major cutaneous soft tissue sarcoma constitued dermatofibrosarcoma protuberans (DFSP) (41.18%). The annual incidence of DFSP is reported as 3 cases per million, population from a population-based cancer registry from 1982-2002 in France [7]. DFSP is a very slowly growing tumor. It may start as a small asymptomatic papule, which is likely ignored. The tumor may gradually enlarge into a lumpy nodule, or it may evolve into an atrophic or sclerotic plaque. Because of the slow progression, the diagnosis is often delayed. DFSP is characterized by its aggressive local invasion. The tumor invades local tissue by extending tentaclelike projections underneath healthy skin rendering complete removal of the tumor very difficult. Incomplete removal of these neoplastic cells results in a high local recurrence rate. Despite the local invasiveness, DFSP rarely metastasizes. The risk for development of metastatic disease is only 5%, including 1% with regional lymph node metastasis and 4% with distant metastasis. Regional lymph node involvement represents a sign of poor prognosis; most patients die within 2 years. The lungs are the most common site of distant metastasis that occurs via hematogenous spread. Usually, metastatic disease is preceded by multiple local recurrences.

Together, these 2 histologic types (KS and DFSP) represented 84.71% of all cases. Excluding Kaposi sarcoma and dermatofibrosarcoma protuberans, the percentage distribution of the remaining cases of cutaneous sarcomas was: angiosarcoma – 5.88%, malignant fibrous histiocytoma – 4.71%, leiomyosarcoma - 2.35% and malignant hemangioendothelioma – 2.35%. Kaposi sarcoma, as well as dermatofibrosarcoma protuberans, was most common among men. The rate ratio of men to women was 1.85 for KS and 2.50 for DFSP.

Cutaneous soft tissue sarcomas differed in terms of anatomic distribution (tab. 3). Head and neck was the most common site for dermatofibrosarcoma protuberans (28.57%) than for other malignant tumors, although DFSP occurred predominantly on the trunk (40.0%) and only 17.14% arose on upper extremity and 14.29% - on lower extremity. Almost half (48.65%) of Kaposi sarcoma lesions arose on the lower

Table 4

Age and sex distribution of patients with cutaneous malignant tumours of mesenchymal origin by histologic type (number of cases)

Histologic type	less than 30		31-40		41-50		51-60		61-70		71-80		81 and over	
	M	W	M	W	M	W	M	W	M	W	M	W	M	W
Kaposi sarcoma			2		4	1	6	4	7	2	3	2	2	4
DFSP	2	1	1	2	6	3	7	2	4	3	4			
Others	3		1	1		1	1	1	1	2	2			

Note: M-men, W-women.

extremities and 37.84% occurred at multiple or overlapping cutaneous sites. Other cutaneous sarcomas, including leiomyosarcoma, angiosarcoma, malignant fibrous histiocytoma, malignant hemangioendothelioma were relatively proportionate in their anatomic distribution.

We observed that Kaposi sarcoma occurred more frequently among men than among women. Kaposi sarcoma increased with age, peaked in the 60s, and subsequently declined. Age-specific KS rates were bimodal, with rates elevated in middle adulthood and at oldest ages for women.

The current study reported that DFSP occurred most commonly during the fifth and sixth decades of life especially among men, whereas the incidence among women rose more modestly after age of 40. The rates for DFSP were higher among men than women during the middle adult years.

The bimodal distribution also was evident among patients with other types of cutaneous sarcomas. The first peak was highest at early ages for men, then the rates were constant across the middle age groups for both men and women and slightly increased in the 70s (tab. 4).

Conclusions

Benign mesenchymal tumors of the skin are much more frequent than their malignant counterparts. Cutaneous soft tissue sarcomas are relatively rare, but they can occur in almost any anatomic site. Most cutaneous soft tissue sarcomas arise, de novo without an apparent causative factor. Clinical signs are painless nodes of a xanthomatous aspect and rapid growth. Early diagnosis is crucial for the prognosis. The etiology of most malignant mesenchymal tumors of the skin is unknown. Genetic, immunodeficiency and environmental factors, as well as viral infections, have been described as associated risk factors. Gene-gene and gene-environment interactions also may contribute to cutaneous soft tissue sarcomas susceptibility. In this study we analyzed the incidence patterns of cutaneous benign and malignant tumours of mesenchymal origin, and observed distinctive differences among the various histologic types and primary sites. Although we had a good sample size in some instances, it was not large enough to allow for sufficient power to estimate rates by stratification. Other limitations include lack of complete data for some patients and of a centralized pathology review of tumors. The strengths of this study are the unbiased ascertainment and assessment of cases of some rare tumors and the fact that it is the first study focused on the epidemiology of cutaneous sarcomas in the Republic of Moldova.

In conclusion, this study has demonstrated that there is variation in cutaneous soft tissue sarcomas incidence patterns over time and by age, sex, and histologic type, supporting the notion that these tumors represent distinct clinical entities, likely because of genetic factors and environmental exposures. More than three-quarters of malignant tumours of mesenchymal origin in skin are represented by Kaposi sarcoma (KS) and dermatofibrosarcoma protuberans (DFSP). Both KS and DFSP rates were highest among men and the age-specific patterns varied by type. Because sarcomas are relatively uncommon and yet comprise a wide variety of different entities, evaluation by oncology teams who have expertise in the field is recommended. Further investigations using large populations and molecular tools are warranted to elucidate the etiology of the diverse spectrum of cutaneous tumors of mesenchymal origin.

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