Etiologic Factors in Soft Tissue Sarcomas

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Key Words

Soft tissue sarcoma · Etiology · Irradiation · Inflammation · Hormones

Summary

Soft tissue sarcomas account for about 1% of all malignancies. The increase in incidence of soft tissue sarcomas during the recent decades may predominantly be attributed to AIDS-related Kaposi's sarcoma; when this tumor is excluded, conclusive evidence for an age-adjusted increase is lacking. Beside the well investigated role of the human immunodeficiency virus 1 (HIV-1) and the human herpesvirus 8 (HHV-8) in the tumorigenesis of AIDS-related Kaposi's sarcoma and several inherited disorders, considerable evidence support a relationship between occupational chemicals as vinyl chloride, phenoxyacetic acid herbicides, chlorphenols, dioxin, medicinal measures as Thorotrast exposure and therapeutic irradiation, and the development of soft tissue sarcoma. Hormones and chronic repair processes are further probably sarcoma-promoting factors. Considering the rarity of soft tissue sarcomas despite the vast portion that soft tissues comprise in the human body, additional knowledge on the tumorigenesis of soft tissue sarcomas might considerably contribute to the understanding of the etiologic pathways of malignant tumors in humans.

Schlüsselwörter

Weichteilsarkome · Ätiologie · Bestrahlung · Entzündung · Hormone

Zusammenfassung

Weichteilsarkome stellen etwa 1% aller bösartigen Neubildungen. Der in den vergangenen Jahrzehnten beobachtete Inzidenzanstieg geht fast ausschließlich auf die rasante Zunahme an AIDS-assoziierten Kaposi-Sarkomen zurück. Bei Außerachtlassung dieses Tumors gibt es bisher keinen schlüssigen Beweis für eine wirkliche alterskorrigierte Häufigkeitszunahme der Weichteilsarkome. Neben der gut untersuchten Rolle des HIV-1-Virus und des humanen Herpes-Virus 8 bei der Entstehung des AIDS-assoziierten Kaposi-Sarkoms und einigen prädisponierenden genetischen Erkrankungen existieren starke Hinweise für einen Zusammenhang zwischen Industriegiften wie Vinylchlorid, Phenoxyessigsäure-Herbiziden, Chlorphenolen, Dioxinen, medizinischen Maßnahmen wie therapeutischer Bestrahlung oder dem Einsatz von Thorotrast, und der Entwicklung von Weichteilsarkomen. Hormone und chronische Reparaturprozesse sind weitere wahrscheinlich fördernde Einflüsse auf die Entstehung von Weichteilsarkomen. Die Tatsache, daß trotz des großen Anteils, den die Binde- und Stützgewebe an der Körpermasse stellen, nur selten maligne Tumoren von diesen Strukturen ausgehen, läßt hoffen, daß ein besseres Verständnis der an der Kanzerogenese von Weichteilsarkomen beteiligten Mechanismen in der Zukunft wichtige Erkenntnisse über die Entstehung menschlicher Tumoren liefern kann.

Introduction

Sarcomas comprise a wide spectrum of tumors. With the different biologic behavior of the sarcoma subtypes and the differences in age, gender, and race distribution [1], it is likely that different and possibly specific etiologic factors are involved in the tumorigenesis of these neoplasms. Due to the rarity of soft tissue sarcomas, a considerable part of the

currently available etiologic data is derived from series with a very small number of events or single case reports.

Incidence

About 1% of malignancies arise from connective or supporting tissue [1, 2]. Among 1,220,100 new cancer cases estimated for

the US in the year 2000, 8,100 cases of malignant soft tissue tumors (0.7%) have been prognosticated [3]. When AIDS-related Kaposi's sarcoma is excluded, both European and US cancer registry data provide no conclusive evidence for an increasing incidence of soft tissue sarcomas [2, 4–6]. Beside the well established relationship between human immunodeficiency virus 1 (HIV-1), several infectious, environmental, occupational, and medical agents have been suspected for an involvement in the tumorigenesis of soft tissue sarcomas.

Inherited Disorders

Several genetically determined syndromes as retinoblastoma, Werner's disease, Li-Fraumeni syndrome, von Recklinghausen's disease, Carney's triad, the lymphedema-distichiasis syndrome and genetically determined immunodeficiency diseases are linked with an elevated risk to develop soft tissue sarcomas [2]. Most families with the Li-Fraumeni syndrome bear mutations of the tumor suppressor gene p53 [2] which is involved in the pathogenesis of a great variety of malignancies and has shown to be linked to sarcoma development in mice [7]. Alterations in the retinoblastoma gene have been found associated both in sporadic and in sarcomas arising in retinoblastoma survivors [2].

Lymphedema

Beside heritable lymphedema, the acquired disease, for instance after treatment of breast cancer, is associated with an increased risk of developing lymphangiosarcoma [2].

Viruses

Before the beginning of the AIDS epidemic, Kaposi's sarcoma was a rare tumor chiefly effecting elderly men [8]. Today, this tumor is common in patients infected with the human immunodeficiency virus 1 (HIV-1) with an up to 70,000-fold increased risk, compared with age- and population-matched controls [8]. Recent evidence suggests that HIV-1 might play a more indirect role in the etiologic process of Kaposi's sarcoma by causing immunosuppression and facilitating co-infection with the human herpesvirus 8 (HHV-8). HHV-8 has been found associated to almost all forms of Kaposi's sarcoma and seems to be a necessary but not sufficient condition for the development of this tumor [2, 8]. Other data, however, support a direct involvement of HIV-1 in the tumorigenesis of Kaposi's sarcoma [8].

Occupational and Environmental Risk Factors

Various occupational and environmental risk factors have been linked to an increased risk of soft tissue sarcoma. There is a well established relationship between herbicides as phenoxyacetic acid derivatives and their highly toxic contaminant 2,3,7,8-tetrachlorodibenzo-paradoxin (dioxin) and the devel-

opment of soft tissue sarcomas [1, 2]. Several studies demonstrated an excess of soft tissue sarcomas in agricultural and forestry workers exposed to phenoxyacetic herbicides and chlorophenols [1, 2] with malignant fibrous histiocytoma and leiomyosarcoma representing the most responsive sarcoma subtypes [1]. Exposure to wood and saw dust has been found associated with an increased risk of leiomyosarcoma [1]. The relationship between the occupational risk factors vinyl chloride and inorganic arsenic and hepatic angiosarcoma is well documented [2, 5, 9]. Abattoir and meat packing workers were found to be at an elevated risk of soft tissue sarcoma [1, 2]. Several hypotheses (packing-associated chemicals, zoonotic oncogenic viruses) have been discussed to explain this phenomenon [2]. Dermatofibrosarcoma protuberans and leiomyosarcoma are sarcoma subtypes found associated with work in a meat packing plant [1].

Hormones

In one study, 4 cases of angiosarcoma of liver have been attributed to the use of androgenic-anabolic steroids for a time period between 15 months and 23 years and with a latent period of 2–35 years from the onset of treatment [9]. One case of hemangiopericytoma has been observed following long-term estrogen treatment in a man [10]. Several epidemiologic, animal experimental, and molecular data suggest an involvement of hormonal stimulation in the tumorigenesis of leiomyosarcoma. In contrast to sarcoma in general, leiomyosarcoma is more common in women than in men, mainly – but not only – due to uterine leiomyosarcoma [2]. Hormone receptors have been found not only in uterine leiomyosarcoma but also in leiomyosarcomas of blood vessels [11, 12]. Gonadal hormones like estrogens stimulate the growth of uterine leiomyomas, and low-grade smooth muscle tumors metastatic to the lung have been shown to regress after oophorectomy [13]. One study showed an excess of uterine leiomyosarcoma and stroma sarcoma in women taking contraceptive drugs [14]. In Golden Syrian hamster, a treatment with androgens combined with estrogens (testosterone propionate / diethylstilbestrol) induced leiomyosarcomas of the uterus, the spermatic cord and the epididymis with a success rate of up to 100% [15]. After transplantation, these tumors are initially responsive to hormones [15]. Hudson et al. [16] demonstrated that the application of testosterone propionate and diethylstilbestrol decreases the expression of a glutathione S-transferase enzyme in the vas deferens of Golden Syrian hamsters. Since the application of testosterone alone results only in hyperplasia of the vas deferens of the hamsters without malignant change, and proliferating cells are known to express lower levels of glutathione S-transferase, which belongs to a superfamily of detoxification enzymes, the authors hypothesized that the androgenic proliferative effect on smooth muscle cells might increase their vulnerability to genotoxic effects [16]. We observed an intratesticular tumor which met all immunohistochemical criteria of leiomyosarcoma in a 32-year-old man 9 years after a 5-year history of high-dose doping with the synthetic androgen 4-chloro-1-dehydro-17a-methyltestosterone (Oral-Turinabol®, VEB Jenapharm, Jena, Thuringia, GDR) as a high-performance

Table 1. Location and involved trauma or inflammatory lesion in malignant fibrous histiocytomas found associated with chronic repair processes: literature review

Author(s), year [ref.]	Location of tumor	Involved trauma or inflammatory lesion
Galli et al., 1977 [35]	bone	medullary bone infarcts
Weinberg & Maini, 1980 [36]	aorta	vascular prosthesis
Lee et al., 1984 [37]	bone	metal implant
Inoshita & Youngberg, 1984 [38]	skin	amputation; hernioplasty
Yamamura et al., 1984 [39]	skin	burn scar
Routh et al., 1985 [40]	skin	chronic ulcer
Lindeman et al., 1990 [41]	bone	shrapnel trauma
Myoui et al., 1991 [42]	pleural cavity	tuberculosis
Staiman et al., 1996 [43]	testicle/spermatic cord	intratesticular injection ^a
Cole et al., 1997 [44]	bone	total hip replacement
Froehner et al., 2000 [45]	bladder	tuberculosis

^a Unethical Nazi medical experimentation at Auschwitz concentration camp.

weight-lifter in the former German Democratic Republic [17–19]. In this case, a possible promoting role of the doping medication was supported by the extreme rarity of intratesticular leiomyosarcoma [20] and the uncommon young age of the patient with leiomyosarcoma preferably affecting the elderly male [21].

Irradiation

The relationship between irradiation and the development of soft tissue sarcomas is well established [2]. The incidence of sarcomas after radiotherapy has been estimated between 0.03% and 0.8% [22, 23]. As among sarcomas found associated with a history of long-standing inflammation, malignant fibrous histiocytoma is the most frequent subtype among irradiation-induced sarcomas [2, 22–24]. Although sarcomas certainly represent only a minority of all radiation-induced neoplasms [25], it has been estimated that about 5% of sarcomas may be attributed to previous irradiation [26]. The diagnosis of an irradiation-induced sarcoma needs histologically proven development of a sarcoma after an appropriate long latent period (3–5 years) in an irradiated area which was without evidence of such tumor before the irradiation [23]. Since low-dose irradiation seems not to increase the risk of soft tissue sarcoma significantly [22, 27], one can speculate that beside the irradiation-induced DNA damage chronic repair processes might be involved in the tumorigenesis of irradiation-induced sarcomas. Various sarcomas, mainly hepatic angiosarcomas, have been observed after application of Thorotrast, a radioactive contrast medium used until the 1950s [2].

Chronic Repair Processes

Although epidemiologic studies did not demonstrate an increased risk of soft tissue sarcomas following hip replacement and silicon breast implant [28, 29], some arguments support a relationship between chronic repair processes and

soft tissue sarcoma. Several implants were effective inducers of soft tissue sarcoma in the animal model with malignant fibrous histiocytoma being the most common subtype [30]. In rodent models, sarcomas were observed after implantation of various polymers, silicone, titanium, nickel-chromium, aluminum oxide [30, 31], silicone elastomer, impermeable cellulose acetate filters [32], methylchloranthrene [33], and dimethyl hydrazine [34]. In view of the wide variety of sarcoma-inducing materials, it has been hypothesized that the tumorigenic effect is mainly linked to physical properties of the implants rather than with chemical characteristics [30]. In humans, malignant fibrous histiocytoma has been found in individual cases after a great variety of chronic repair processes (table 1) and is the most commonly observed subtype in this setting [38, 40]. The carcinogenic pathways involved are poorly understood. Despite a conceivable tendency of physicians and patients to seek explanations for tumor growth which might influence the attribution of tumors to previous trauma or inflammatory lesions in the literature, it seems likely that the association between chronic repair processes and the development of soft tissue sarcoma is more than coincidental [38, 40].

Conclusion

Beside the well investigated role of HIV-1 and HHV-8 in the tumorigenesis of AIDS-related Kaposi's sarcoma and several genetically determined disorders, considerable evidence supports a relationship between occupational chemicals as vinyl chloride, phenoxyacetic acid herbicides, chlorophenols, dioxin, medicinal measures as Thorotrast exposure and therapeutic irradiation, and the development of soft tissue sarcoma. Hormones and chronic repair processes are further probably sarcoma-promoting factors. Considering the rarity of soft tissue sarcomas despite the vast portion that soft tissues comprise in the human body, additional knowledge on the tumorigenesis of soft tissue sarcomas might significantly contribute to the understanding of the etiologic pathways of malignant tumors in humans.

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Erratum

Im Abstract-Band ONKOLOGIE 2000;23 (Sonderheft 7) zur Gemeinsamen Jahrestagung der ÖGHO/DGHO, Graz, Oktober 2000, sind auf Seite 93 für die Abstracts Nr. 345 und 346 versehentlich die Autoren nicht korrekt benannt.

Wir bitten zu beachten, dass die Autoren beider Abstracts *C. Zang* und *P.E. Petrides* sind.