Primary Sarcomatoid Tumor of the Bladder: A Different Entity but the Same Approach?

Javier Molina-Cerrillo,[1] Olga Martínez-Sáez,[1] Teresa Alonso-Gordoa,[1] Pedro Tirado-Zambrano,[2] Beatriz Delgado-Vargas,[3] Julie Earl,[4] Enrique Grande[1]

Abstract

Bladder cancer remains a frequent cancer worldwide, and most tumors are diagnosed at localized stages. Urothelial carcinoma (UC) accounts for 90% of bladder cancer cases. Sarcomatoid carcinoma (SaC) of the bladder is a rare variant (0.5% of total bladder cancers) characterized by 2 components based on histology; the epithelial and mesenchymal phenotypes, which can be easily differentiated by immunohistochemistry. SaC has similar epidemiologic features to UC but different behavior, aggressiveness, and prognosis. In this review, we summarize the main differences between UC bladder cancers and SaC subtypes. The therapeutic strategies used in SaC today do not differ much from those used for the urothelial variant. However, there is still no standard treatment—the result of a lack of clinical trials for the sarcomatoid variant. Further multicenter comparative studies are needed to devise a better treatment strategy for patients with this rare histologic tumor subtype.

Clinical Genitourinary Cancer, Vol. 13, No. 6, 493-8 © 2015 Elsevier Inc. All rights reserved.
Keywords: Bladder, Molecular, Multimodal treatment, Sarcomatoid, Urothelial

Introduction

Several completely different tumor entities are included under the umbrella of the term "bladder cancer," classified depending on their molecular and clinical behavior. Transitional cell carcinoma or urothelial carcinoma (UC) of the bladder is the most frequent subtype and is thus the one referred to with the term "bladder cancer."[1-3] Despite the significant incidence of these tumors, no new systemic therapies for UC have been approved by the US Food and Drug Administration in the last couple of decades. Other tumor histologies arising from the wall of the bladder are less known to physicians in the genitourinary field; however, these types have followed the same local and systemic approaches used for UC.[4-6] This is also the case for sarcomatoid carcinoma (SaC) of the bladder, a subtype with a different molecular profile and a different response to available systemic treatments. In this review, we summarize the main differences in epidemiology, histology, molecular profile, and systemic management of common UC bladder cancer compared to SaC.

[1]Medical Oncology Department
[2]Pathology Department
[3]Surgery Department
[4]Molecular Biology Laboratory, Medical Oncology Department
Ramón y Cajal University Hospital, Madrid, Spain

Submitted: Feb 14, 2015; Revised: Apr 21, 2015; Accepted: May 4, 2015; Epub: May 13, 2015

Address for correspondence: Enrique Grande, MD, PhD, Servicio de Oncología Médica, Hospital Ramón y Cajal, Carretera de Colmenar km 9,1, 28034-Madrid, Spain
Fax: +34913368263; e-mail contact: egrande@oncologiahrc.com

Epidemiology

Bladder cancer is the most common malignancy of the urinary tract and the seventh most common cancer worldwide, with an estimated 260,000 new cases occurring every year in men and 76,000 in women.[1,3] It accounts for about 3.2% of all cancers worldwide. The highest incidence rates of bladder cancer are observed in Western Europe, North America, and Australia. In the European Union, the age-standardized incidence is 27 per 100,000 population in men and 6 per 100,000 population in women.[1,3]

According to the histology, approximately 90% of the patients with bladder cancer have UC, whereas 5% have squamous cell carcinoma, 1% to 2% adenocarcinoma, and smaller percentages other histologic variants of UC, such as primary small cell carcinoma, micropapillary tumors, and lymphoepithelioma-like tumors, among others. SaC is a rare entity that represents only a small proportion of all bladder cancers (< 0.5%).[3-7]

Risk Factors

There are several known and potential risk factors for UC bladder cancer; tobacco is the most important one among many. Other known risk factors for UC include occupational exposure to aryl amines, polycyclic aromatic hydrocarbons, chlorinated hydrocarbons; and exposure to ionizing radiation and to cyclophosphamide.[8-10] Genetic predisposition plays an important role in UC genesis, especially by modifying susceptibility to other risk factors.[9,11] Etiologic factors are largely unknown in patients with SaC

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2015.05.001

because details concerning previous conditions and patient treatments have been scarcely reported and usually focus on describing the exposure to cyclophosphamide therapy or previous radiotherapy.[5,12,13]

Clinical Presentation

The median age at diagnosis for UC is 73 years,[5] which is similar to that for SaC (approximately 70 years).[4-6,14] The male-to-female ratio is almost 3:1 for UC, which is analogous to the ratio of SaC.[3,4,6]

The most common presenting symptom in patients with UC and SaC is asymptomatic microscopic or gross hematuria, similar to other types of bladder cancer. Pain related to advanced local disease and symptoms due to disease spread seem to be more frequent in SaC patients.[1,2,5,6,14-17]

At diagnosis, more than 75% of UC are localized and not muscle invasive[2,7,14]; however, the largest ever reported series showed that only 28% of SaC tumors are diagnosed as localized stages, while 56% showed regional spread and 17% were accompanied by distant metastases.[4,5,7,18]

Histology

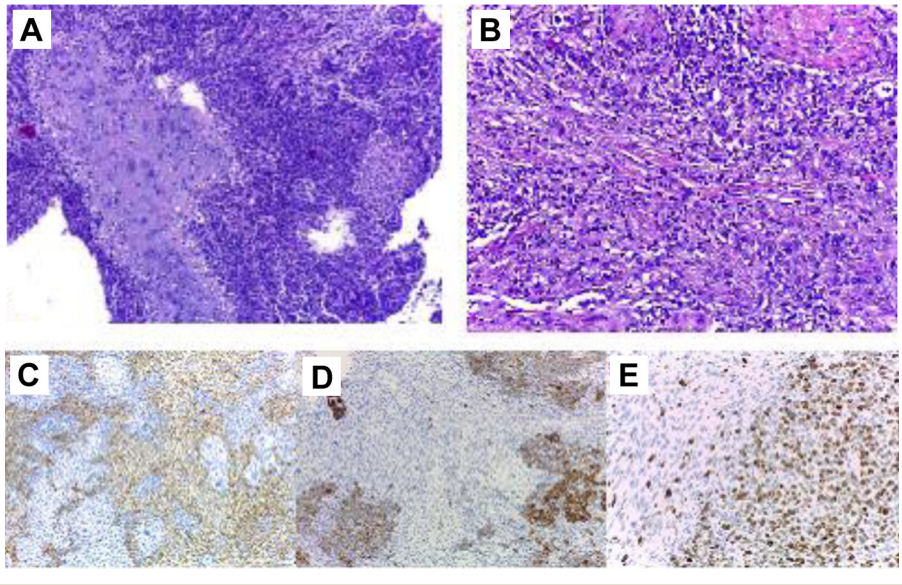
Infiltrative carcinomas show papillary, polypoid, nodular, solid, and ulcerative or transmural diffuse growth. They might be solitary or multifocal tumors. The histology of infiltrating UC is variable. Most pT1 cancers are papillary and are of low or high grade, whereas most pT2-T4 carcinomas are nonpapillary and of high grade. These carcinomas are graded depending on some architectural characteristics and the degree of nuclear dysplasia.

There is considerable disagreement in the literature regarding the nomenclature and histogenesis of these tumors. In some series, both carcinoma and SaC are included as sarcomatoid carcinoma. In others, they are regarded as separate entities. The term "sarcomatoid carcinoma" is used for malignant spindle cell neoplasms in which epithelial differentiation may be demonstrated by immunohistochemical or ultrastructural studies; the term "carcinosarcoma" is used for malignancies characterized by an intimate admixture of malignant epithelial elements (carcinoma) and malignant soft tissue elements (pure sarcoma).[3,5] Pathologists have largely discarded the notion of distinguishing between the 2 tumor types, as both are rapidly growing polypoid neoplasm that confer similar prognosis. The overlap in clinical features suggests that these 2 entities are variations of the same neoplastic transformation process.[16] In an attempt to eliminate all this confusion related with terminology, the 2004 World Health Organization classification of urothelial neoplasms defines SaC as all biphasic malignant neoplasm with evidence of epithelial and mesenchymal differentiation (Figure 1A).[3,16]

The gross appearance of these tumors is characteristically sarcoma-like: dull gray with infiltrative margins. These tumors are often polypoid or a large, broad-based solid mass, often edematous, with foci of hemorrhage, necrosis, and ulceration, and with extension into the muscular layer.[3,6,15,16]

Microscopically, SaC is composed in most cases of an epithelial component consisting of high-grade UC with possible glandular or a

Figure 1 **Results of Histology. (A) Hematoxylin and Eosin–Stained Section of SaC Showing the Epithelial Component Together With Heterologous Elements (in This Case, Cartilage). (B) SaC. Hematoxylin and Eosin–Stained Section Revealing a Spindle Cell Component. (C) Immunohistochemical Staining for Vimentin Shows its Positivity for the Stromal Component. (D) Immunohistochemical Staining for Cytokeratin 7 (CK7). Positive Stain for the Epithelial Component of SaC. (E) Numerous Tumor Cell Nuclei Stain Positive With Ki-67 Monoclonal Antibody, Showing a High Proliferation in Both Mesenchymal and Epithelial Components**



Abbreviation: SaC = sarcomatoid carcinoma.