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Review Article

Clear Cell Urothelial Carcinoma of the Bladder Associated with Adenocarcinoma of the Prostate – Case Report and Literature Review

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2. Keywords

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1. Abstract

The association of Clear Cell Variant of Urothelial Carcinoma (CCVUC) of the bladder with other urogenital tumors and, especially, with prostate adenocarcinoma, is extremely rare and confers additional complexity with regard to diagnosis and treatment. A 68-year-old male patient has been subjected to total cystectomy with bilateral ureterocutaneostomy. The postoperative evolution was unfavourable, leading to irresuscitable cardiopulmonary arrest. The histopathological examination established the coexistence of vesical CCVUC and acinar prostatic adenocarcinoma. The immunoprofile of the clear cell neoplastic proliferation revealed positivity for cytokeratin 7, cytokeratin 20 and CEA (carcinoembryonic antigen). The use of cytokeratin 34βE12 shows negative reaction in the prostatic malignant glandular structures that are immunopositive for PSA (prostate-specific antigen). The comparative evaluation, based on clinical, microscopic and immunophenotypical criteria, with other clear cell epithelial or nonepithelial, primary or secondary neoplasms, outlines the profile of WHO-recognized CCVUC and is mandatory for the adequate therapeutic approach. The analyzed CCVUC case is in agreement with those reported so far regarding male gender predilection, histopathological features, immunoexpression, advanced stage at diagnosis and discloses an unfavourable clinical outcome. The CCVUC characterization in terms of prognosis is still incomplete and requires thorough studies on representative batches of cases. Molecular CCVUC evaluation represents the perspective for the accurate tumoral description and, subsequently, for refining therapeutic protocols.

3. Introduction

Urothelial carcinoma represents the most common form of malignant tumor of the urinary tract. The 2016 WHO Classification of Tumours of the Urinary System includes, in addition to well-characterized types of urothelial carcinoma, newly introduced morphological classes, among which the Clear Cell Variant of Urothelial Carcinoma (CCVUC) constitutes a distinct category [1]. CCVUC is a rare form of urinary bladder malignancy who's biological behavior is incompletely explored to date [2]. Currently, 16 cases are reported in the literature [2, 3, 4,5].

During the evolution of the study of this particular neoplasm, major variations regarding the gender distribution are noted. According to some authors, this peculiar form of urothelial carcinoma mainly affects the female adults, at a mean age of 53 years [6]. Other researchers report a male: female ratio of 1:1 and a median age of 67.2 years [7]. A recent study highlights the predominant male involvement (male: female – 12:1), with an average age of 71.5 years [4]. The clinical presentation is dominated by hematuria; anuria, frequency, urgency, dysuria or other lower urinary tract symptoms are seldom encountered [2-4, 7-14].

The existence of synchronous urogenital malignant tumors is reported in the literature, where cases of triple neoplasms (renal cell carcinoma; transitional cell carcinoma of the renal pelvis, ureter and urinary bladder; adenocarcinoma of the prostate) are highlighted, some of the patients having the particularity of exposure to the atomic event in Hiroshima [15, 16]. Nevertheless, the association of vesical CCVUC with other urogenital tumors and, especially, with a prostate adenocarcinoma, is extremely rare, being reported so far by two research papers [3, 8]. The coexistence of CCVUC and prostatic adenocarcinoma confers additional complexity with regard to diagnosis and treatment.

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The aim of this study is to present a case of CCVUC of the urinary bladder associated with an incidentally discovered prostate adenocarcinoma, to perform a comprehensive differential diagnosis with other clear cell neoplastic entities and to evaluate the prognosis, based on a review of the literature. The histogenesis of clear cell tumors is very various and, in many cases, the microscopic features are overlapping, which leads to the idea that establishing a correct diagnosis is crucial for the initiation of a proper therapeutic protocol [7].

4. Materials and Methods

4.1. Case Report

A 68-year-old male patient, known with a history of urological malignancy (diagnosed with urothelial carcinoma 5 months prior to the current presentation) and multiple chronic cardio-pulmonary associated diseases, presents in the Emergency Room of the County Clinical Hospital of Constanta for gross hematuria, complete retention of urine, malaise, right back pain. The patient is hospitalized in the Department of Urology for further investigations and therapy. Imagistic evaluation (computed tomography scan) detects a grade-II right ureterohydronephrosis, secondary to right ureteral orifice obstruction by tumoral extension of an 8x2.3 cm bladder neoplasm. For this purpose, cystoscopy is performed, with an attempt of endoscopic tumor removal by Transurethral Bladder Resection (TURBT) that fails due to the tumor volume. Later, after an interval of four days, during which the patient is rebalanced with fluids and electrolytes, total pelvi-retroperitoneal cystectomy with bilateral ureterocutaneostomy is practiced. The postoperative evolution is unfavorable, leading to irresuscitable cardiopulmonary arrest.

The morphological analysis of the surgical specimens indicates the existence of particular histopathological forms and of surprising lesional associations.

The processing of the TURBT and cystectomy specimens is made in the Clinical Service of Pathology in successive standard stages: fixation in 10% formaline, paraffin-embedding, sectioning at 5-µm, staining with Hematoxylin–Eosin (HE) and Periodic Acid-Schiff (PAS). Additionally, an immunohistochemical evaluation is performed using several monoclonal antibodies:

- monoclonal mouse anti-human cytokeratin 7, clone OV-TL 12/30 (DAKO) – it highlights the presence of Cytokeratin 7 (CK7), found in multiple locations (transitional epithelium, lung, renal collecting ducts, uterine cervix, mesothelium, breast glandular epithelium, bile ducts); most cases of urothelial carcinoma present the immunoreaction for CK7 [17];
- monoclonal mouse anti-human cytokeratin 20, clone Ks20.8b (DAKO) – it reveals the presence of cytokeratin 20 (CK20), existing in the digestive and transitional epithelium, and in the cutaneous Merkel cells; the immunolabeling of CK20 in urothelial carcinoma is variable, ranging from 15% to 97% [17];
- monoclonal mouse anti-human Carcinoembryonic Antigen (CEA), clone II-7 (DAKO) – positive in the clear cell variant of the urothelial carcinoma [7];
- monoclonal mouse anti-human cytokeratin, high molecular weight, clone 34βE12 (CK34βE12) (DAKO) – useful for the detection of myoepithelial and basal cells [17];
- Prostate-Specific Antigen (PSA), clone ER-PR8 (DAKO) – a glycoprotein found almost exclusively in the prostatic epithelium; positive immunoreaction in normal, hyperplastic and malignant lesions of this tissue [17].

The applied immunohistochemical techniques are compliant with the recommendations of the manufacturer (DAKO).

The patient expressed, by signing the informed consent, the agreement regarding the use for scientific purpose of medical data and microscopy images.

5. Results and Discussions

The pathological analysis reveals interesting aspects. Tumoral fragments sampled by TURBT, measuring overall 8x4.5x1 cm, are gray-yellow in appearance and of low consistency. The microscopical features are compatible with the diagnosis of infiltrative high-grade urothelial carcinoma (G3), associated with large areas of clear cell carcinoma and with marked necro-inflammatory phenomena.

The cystectomy specimen of 14x8.5x4.5 cm shows a bladder cavity occupied on the right lateral and superior wall by a 6x4.5x3 cm exophytic and solid-nodular, friable mass of heterogeneous aspect, due to the coexistence of gray-white areas alternating with brown-black zones; the wall is infiltrated, thickened up to 2 cm, with the involvement of the external surface; the section reveals a yellowish-white variegated appearance, of increased consistency; at the bladder neck, the wall is 1.5 cm thick, with whitish firm cut surface. The restant mucosa presents a slightly mamelonated, grayish aspect. Microscopically, the cystectomy specimen exhibits histopathological lesions of infiltrative high-grade urothelial carcinoma (G3), accompanied by wide zones of clear cell carcinoma and by important necro-inflammatory changes. The architecture of the neoplastic population is characterized by a solid and alveolar pattern (Figure 1). The clear cells constituting up to 90% of the tumoral volume, present abundant PAS-positive cytoplasm. The hyperchromatic nuclei are pleomorphic with conspicuous nucleoli (Figure 2). The malignant proliferation penetrates transmurally, extending into the perivesical adipose tissue and invading the right ureteral orifice. Perineural Infiltration (PNI1) and involvement of

the Lymphovascular spaces (LVI1) are also noted. Surgical margins of urethra, ureters and perivesical soft tissue are uninvolved by invasive carcinoma. The adjacent mucosa reveals lesions of urothelial dysplasia and carcinoma in situ.

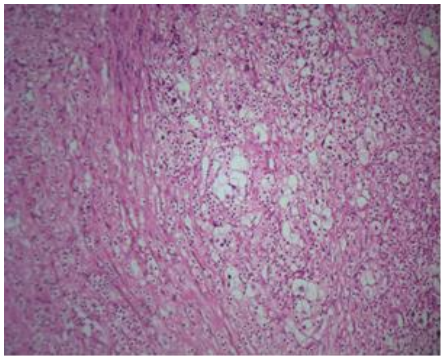

Figure 1: Clear cell variant of urothelial carcinoma with solid and alveolar pattern (H.E.X100)

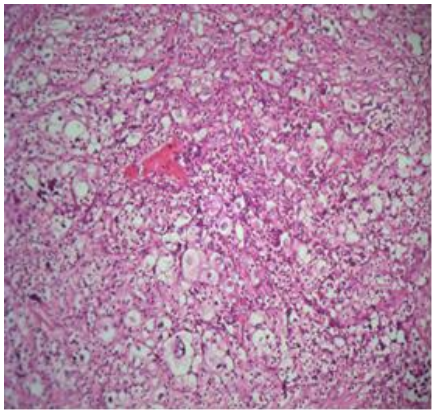

Figure 2: Malignant cellular population with clear cytoplasm and pleomorphic nuclei (H.E.X200)

The examination of the tissular fragments originating from the bladder neck discovers the presence of prostatic type glands, accompanied by crowded microglandular structures, with infiltrative character, suggestive for the diagnosis of acinar prostatic adenocarcinoma (Figure 3). Lymph nodes were not identified in the submitted specimen.

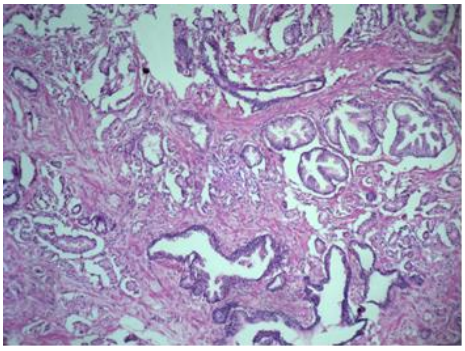

Figure 3: Prostatic tissue with crowded microglandular infiltrative structures (H.E.X200)

The immunohistochemical evaluation of the clear cell neoplastic proliferation of the bladder reveals positive reactions for CK7, CK20 and CEA (Figures 4, 5, 6).

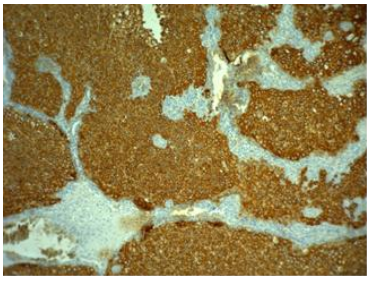

Figure 4: Positive reaction for CK 7 (X200)

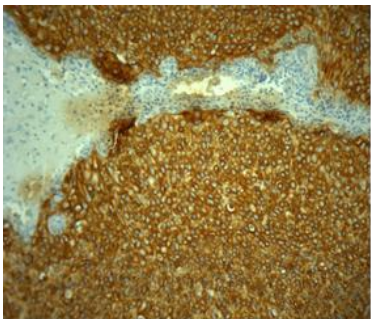

Figure 5: Positive reaction for CK 20 (X200)

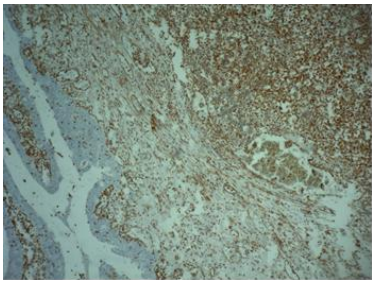

Figure 6: Positive reaction for CEA in clear cell variant of urothelial carcinoma (X100)

The histopathological picture correlated with the results of the immunohistochemical evaluation are consistent with the diagnosis of CCVUC.

In order to investigate the biological potential of prostatic glandular structures, the application of CK34βE12 has the following results: positive reaction in the basal cells of the normal prostate glands and negative reaction in the invasive glandular lesions. PSA reveals a positive immunoreaction, both in the normal prostatic ducto-acinar epithelium and in the malignant microglandular structures, which confirms the prostatic origin of the adenocarcinoma (Figure 7).

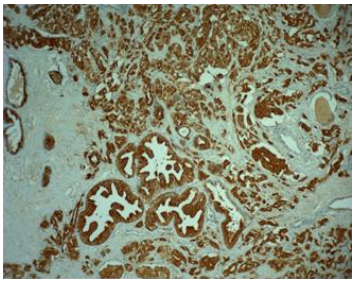

Figure 7: Positive reaction for PSA in normal and malignant prostatic structures (X200)

The incidental discovery of prostate adenocarcinoma on the surgical specimen determines the diagnosis of synchronous malignant tumors: vesical CCVUC (pT3 LVI1 PNI1, G3) and prostatic acinar adenocarcinoma (Gleason score 7=3+4), grade group 2 (World Health Organization 2016) [18].

According to the current data from the specialty literature, the histopathological features of CCVUC are characterized by the focal or diffuse presence of clear cells with rich glycogen-containing cytoplasm, distinct cellular outlines and high-grade nuclei (karyomegaly, hyperchromasia, irregular nuclear membrane, intense mitotic rate), associated to a high-grade urothelial carcinoma [6, 19]. An important element is specified by studies that add as a diagnostic criterion the proportion of 30-90% of clear cells from the total malignant population [3, 14]. The architectural pattern of the neoplastic proliferation is massive and alveolar [7, 20]. Histochemically, the intracytoplasmic glycogen is highlighted by the PAS staining. The immunohistochemical profile of the CCVUC is described by the positive reaction for CK7, CK20, CK34βE12, tumor protein p63, thrombomodulin; negative reaction for vimentin, Renal Cell Carcinoma marker (RCC), PSA, paired-box 2 (PAX2), prostein (P501S), Prostate-Specific Membrane Antigen (PSMA) [6]. It is important to underline the immunoexpression for CEA in clear cells [7, 21]. The current case fulfils the microscopical criteria and the main immunohistochemical features of CCVUC.

The histogenesis of this type of neoplasm is mesonephric, the evidence of this differentiation being sustained by researchers [14]. From the anatomo-clinical point of view, CCVUC is usually unifocal, similar with the presented case, involving, in descending order of frequency, the left lateral bladder wall, followed by the right one, with variable extension to the anterior, posterior, superior or inferior portions of the vesical wall [2-4, 7, 8, 10-12]. One case report presents primary multiple lesions of the bladder, in form of three exophytic tumors [13]. Grossly, the appearance of CCVUC may be nodular, cystic, infiltrative, papillary or non-papillary vegetant [13]. Analyzing all the communicated cases, this peculiar form of urothelial carcinoma is diagnosed in advanced stages, most frequently pT3, followed by pT2 and pT4, respectively [2-4, 7-9, 12, 14, 22]. The current case falls within the characteristics of the CCVUC series documented so far: location on the right latero-superior wall of the bladder, exophytic and nodular aspect, pT3 stage.

The presence of clear tumoral cells requires their differentiation from other malignant proliferations with apparently similar characteristics. The main distinction must be made from the Clear Cell Adenocarcinoma (CCA) of the bladder. The histogenesis of this tumoral type has been debated by several theories. Some authors have explored the urothelial origin of clear cell adenocarcinoma, based on morphological, immunohistochemical and cytogenetic investigations [23-25]. The researchers base on the idea of divergent glandular differentiation of transitional neoplasms, supported by the observation of the coexistence of conventional urothelial carcinoma with CCA [24, 26, 27]. Another hypothesis suggests the derivation from müllerian structures of the bladder, due to the predominant involvement of women, the association with müllerian elements of benign nature, the microscopical resemblance with clear cell adenocarcinoma of the female genital tract and the controversial expression for cancer antigen 125 (CA125) [21, 23, 24, 28-31]. A distinct theory presents the possibility of mesonephric origin for this neoplasm, but scientific data supporting this idea are insufficiently grounded [23-25, 32, 33]. The supposition of the non-mullerian derivation of bladder adenocarcinoma is also mentioned [24, 25]. Another presumption refers to the possible carcinogenic connection between nephrogenic metaplasia/adenoma and CCA, based on histopathologic and cytogenetic observations [21, 25, 34, 35]. The architectural features of CCA reveal a marked complexity, due to the coexistence of tubules, cysts, solid areas and small papillae with hyalinized axis covered by an unstratified cellular layer. Citologically, the most evident trait consists in the presence of hobnail cells, associated with a flattened, cuboidal or columnar cellular population with eosinophilic or clear glycogenated cytoplasm, moderate/severe nuclear atypia and marked mitotic activity [6, 20, 23, 25, 36]. The immunohistochemical features of CCA of the bladder consist in immunoreactivity for CA125, CK7, CEA, cytokeratin CAM 5.2, 34βE12, PAX2, paired box 8 (PAX8), Alpha-Methyl-Acyl-Coenzyme a racemase (AMACR), tumor suppressor p53; negative reaction for PSA, p63, Estrogen Receptor (ER), Progesteron Receptor (PR), CK20 (occasionally positive) [6, 21, 24, 37]. The distinction from CCVUC is based on immunohistochemical methods combined with morphological elements, comprising the observation of a more diffuse architecture in CCVUC, accompanied by foci of conventional urothelial carcinoma [20]. In rare cases of CCVUC exhibiting papillary areas, these structures have thin cores and hobnail cells are absent [37].

The WHO category represented by the lipid-rich variant of urothelial carcinoma includes lipoblast-like malignant epithelial cells, with eccentrical nucleus indented by single or multiple clear cytoplasmic vacuoles [38, 39]. PAS and mucin stains (alcian blue, mucicarmine) are negative; conversely, oil red O confirms the lipid composition of the vacuoles [3, 39, 40]. This uncommon variant of transitional neoplasm constitutes 10-50% of the tumoral volume, is always accompanied by high grade conventional urothelial carcinoma and has the following immunoprofile: positive for CK7, CK20, CAM 5.2, CK34βE12 and pancytokeratin AE1/AE3, Epithelial Membrane Antigen (EMA) and thrombomodulin; negative for vimentin and S100 protein [39]. Differentiation of this peculiar type of neoplasm from CCVUC is possible on morphological and histochemical bases, allowing the observation that PAS-positive clear cells do not exhibit a lipoclastic appearance.

Another histopathological entity which must be distinguished

from CCVUC is the synchronous or metachronous bladder metastasis from clear cell Renal Cell Carcinoma (RCC) [40, 41]. A variable proportion of 0.3-1.6% of RCC cases determine bladder metastasis, that are regarded as less than 2% of all vesical neoplasms [40, 42-45]. The pathways of malignant spread are multifarious: hematogenous, lymphatic route, direct extension and endoluminal implantation [40, 45]. The differentiation from CCVUC is accomplished by correlating the clinical and imagistic data that indicate the existence of a tumoral mass in the kidney and, possibly, the presence of metastases in multiple organs. From the morphological point of view, clear cell RCC has a preponderant alveolar pattern of growth, separated by connective septa with a well-developed network of blood vessels [20]. The cellular population is polygonal with well-defined cell membrane, clear cytoplasm and different degrees of nuclear pleomorphism, according to grading of primary RCC. The immunohistochemical features supporting the diagnosis of RCC and its distinction from CCVUC are the cytokeratin-vimentin co-expression, the positive reactions for RCC marker, CAM 5.2, PAX2 and the negative reactivity for CK7, CK20, CEA [7, 20, 21]. However, it should be noted that there are reported cases of bladder CCVUC associated with clear cell RCC, which further complicates the differential diagnosis of CCVUC with an RCC metastasis [7, 22]. The observation of the existence of clear cells in both lesional entities may be the premise of an in-depth research of molecular biology and genetics, in order to detect mutational abnormalities common to the two neoplasms.

The exclusion of bladder invasion from a prostatic carcinoma is based on the morphological characteristics of the prostate neoplasm: the polymorphous architecture (acinar, massive, cribriform), relatively uniform nuclei with conspicuous nucleoli, cytoplasm with eosinophilic, clear or foamy appearance [20]. Immunohistochemically, the prostate carcinoma is positive for PSA, Prostatic Specific Acid Phosphatase (PSAP), P501S, PSMA and negative for CK7, CK20, thrombomodulin, p63, CK34βE12 [20]. The urothelial carcinoma presents opposite reactions for these markers [20].

The detailed review of the distinguishing criteria with the main clear cell neoplasms must be supplemented by mentioning the categories of nonepithelial tumors that are suitable for differential diagnosis of CCVUC. An interesting comment is the one regarding paraganglioma, a rare tumor originating from paraganglion cells of the bladder wall, with particular clinical, histopathological and immunophenotypic profile. The distinctive, but inconstantly present symptoms are related to micturition and expressed by hypertension, headache, anxiety, syncope, sweating, hematuria, associated with possible urinary detection of vanillylmandelic acid [46]. Groups ("zellballen") of large polygonal cell with abundant eosinophilic granular cytoplasm and monomorphic nuclei, surrounded by delicate stroma, represent the microscopical hallmark of this neoplasm [46]. Occasionally, the tumoral population displays a sheet-like growth pattern, zonal presence of clear cells, nuclear atypia and necrosis [47]. These elements could lead to diagnostic confusion with CCVUC, mostly on TURBT specimens. The distinction is based on neuroendocrine markers, that are positive in paraganglioma and negative in CCVUC, the latter being CK7 positive and often accompanied by in situ urothelial carcinoma [46, 47].

A particular lesion is clear cell myomelanocytic tumor, an infrequent perivascular epithelioid cell neoplasm of the urinary bladder, composed of nests of clear to eosinophilic epithelioid cells in a slender vascular stroma [48]. Immunohistochemistry aids in the distinction from CCVUC, the neoplastic cells being positive for human melanoma black HMB-45, smooth muscle actin and negative for S100 protein, melan-A, desmin, and pancytokeratin [48]. The differential diagnosis of CCVUC should also include vesical metastases of melanoma, clear cell sarcoma and seminoma, which are excluded on clinical, imaging and immunohistochemical bases [3, 4].

The particularity of the presented case consists in the diagnosis of a rare form of urothelial carcinoma – CCVUC – and in the incidental discovery of the association with prostate adenocarcinoma. CCVUC diagnosis was based on the observation of its morphological features: the presence of cells with clear PAS-positive cytoplasm, pleomorphic nuclei and sheet-like disposition, associated with areas of conventional urothelial carcinoma; absence of glandular differentiation and of hobnail cells. The immunohistochemical phenotype of the tumor corresponds to that of a urothelial carcinoma: positivity to CK7, CK20, CEA. Regarding the association with a prostate adenocarcinoma, there were no assumptions concerning the prostatic origin of clear cell bladder carcinoma, since prostatic neoplasm has a PSA-positive acinar pattern, while tumoral proliferation of the bladder has a solid configuration and a urothelial immunoprofile.

Considering the unfavorable evolution of the patient, undoubtedly determined by the consequences of the rapid progression of the bladder carcinoma, it can be stated that CCVUC has an aggressive biological potential. This assertion is consistent with the observations of other researchers, who reported the death of the patients diagnosed with CCVUC after a survival time of 20 months [8], 5 months [4], 4 months [49] and 14 weeks, respectively [2]. There are authors that have described other cases of CCVUC, some of them without tumor recurrence after a variable follow-up period [3, 7, 9, 10, 12-14, 22].

The therapeutic algorithm of CCVUC is incompletely defined, due to the low number of cases reported so far. According to current data from the literature, the outcomes after the performance of surgical procedures (TURBT or radical cystectomy) were variable [4,

5, 14, 49]. The adjuvant chemotherapy was inconstantly used [8, 13]. Information related to the trimodality therapy, consisting in TURBT or partial cystectomy and concurrent radio-chemotherapy are not accessible [5, 50, 51].

An avant-garde direction in the detailed study of urothelial carcinomas and, implicitly, of CCVUC, is represented by contouring of molecular profiles in the form of the following subtypes: luminal, luminal-papillary/uroA, luminal-infiltrated/p53-like, basal-squamous, basal-neuronal, basal mesenchymal-like/claudin-low type [5, 52-54]. From the existing data, luminal or basal types are assigned to CCVUC [5]. Basal profiles exhibit a more aggressive biological potential than luminal subtypes, with unfavorable prognosis, but show sensitivity to neoadjuvant chemotherapy [5].

6. Conclusions

The exceptionally rare association of an infrequent variant of urothelial carcinoma and a malignant prostatic neoplasm attributes an original character to the presented case, which generates an in-depth analysis regarding the differential diagnosis. Concurrent existence of CCVUC and prostate adenocarcinoma does not raise difficulties in diagnosis, because the massive pattern of the bladder tumor noticeably contrasts with the acinar architecture of the prostate adenocarcinoma. In addition, the immunohistochemical examination certifies this distinction. The comparative evaluation, based on clinical, microscopic and immunophenotypical criteria, with other clear cell epithelial or nonepithelial, primary or secondary neoplasms, outlines the profile of the WHO-recognized CCVUC and is mandatory for the adequate therapeutic approach.

The analyzed CCVUC case is in agreement with those reported so far regarding male gender predilection, histopathological features, immunoexpression, advanced stage at diagnosis and discloses an unfavorable clinical outcome. The CCVUC characterization in terms of prognosis is still incomplete and requires thorough studies on representative batches of cases. Molecular CCVUC evaluation represents the perspective for the accurate tumoral description and, subsequently, for refining therapeutic protocols.

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