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Clinical Study

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Carcinosarcomas and epithelial to mesenchymal transition (EMT)

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Abstract

Carcinosarcomas are rare, extremely aggressive malignant neoplasms, combining two cellular epithelial and sarcomatous components. Epithelial to mesenchymal transition (EMT) is a biological process that occurs in malignant tumors. Sarcomatous component in carcinosarcomas is derived from the carcinomatous component as a result of metaplasia/transdifferentiation (EMT). We present the pathohistological characteristics and immunohistochemical analysis of four clinicalcarcinosarcoma cases with a different primary localization. Our main goal is to present the classic pathohistological picture of EMT and the role of intermediate filament (IF) proteins in cell and tissue structural integrity, as well as their importance for local invasion and distant hematogenous metastases in carcinosarcomas.

Keywords: Carcinosarcoma, Epithelial to Mesenchymal Transition, Sarcomatous Cell Component, Intermediate Filament Proteins, Vimentin

Introduction

Carcinosarcomas are rare, aggressive biphasic, malignant tumors with malignant epithelial (more frequently high grade carcinoma) and sarcomatous (can be homologous and heterologous) components [1,2]. Sarcomatoid carcinomas are biphasic tumors consisting of a nonsmall cell carcinoma with heterologous sarcomatoid differentiation [3]. Sarcomatous component in carcinosarcomas is derived from the carcinomatous component as a result of metaplasia/transdifferentiation (epithelial to mesenchymal transition) [1]. Epithelial to mesenchymal transition (EMT) is a reversible biological process in which epithelial cells lose their unique features of apicobasal polarity, epithelial markers, intercellular junctions, reorganization of the cytoskeletal architecture, immobility and differentiation and redirect to mesenchymal phenotype with the ability to migrate and invade [4]. We consider and analyze at four carcinosaromas pathohistological characteristics along with their immunohistochemical analysis. In this way we will present the classic picture of EMT and the role of intermediate filament (IF) proteins in the cellular and tissue structural integrity, as well as their importance in the invasion and metastasis of carcinosarcomas.

Clinical Cases

Clinical Case No 1

Presents a woman 55 years old. For 2-3 months he has complained of easy fatigue and difficulty breathing in mild physical exertion, dizziness and tenderness in the right thoracic half. Reports a constant irritating cough with phlegms without blood. She lost 10 pounds for three months. Radiography of the lung detects a tumor in the right lung, which is why it is aimed at fibrobronchoscopy with a biopsy. Histological examination reports a classic malignant biphasic cellular growth model with poorly defined tubular structures, lined with single or more layers of hyperchromatic cells (undifferentiated epithelial component) surrounded by undifferentiated mesenchymal tissue consisting of oval to spindle -shaped cells with hyperchromatic nuclei (mesenchymal component). There is a cellular variety involving cells of different sizes, as well as giant cells with whimsical multiple nuclei with atypical mitoses resembling tumor cells originating in muscle tissue, as well as cells with vacuoized nuclei, histiocyte like cells, atypical cells with hyperchomatic nuclei and bizarre tumor cells with foamy cytoplasm and pronounced atypical characteristic against the background of collagen stroma (Figure 1).

Immunohistochemistry (IHC):p63-focal positive IHC expression in single epithelial undifferentiated tumor cells; TFT1-focal positive expression in the epithelial tumor component; Vimentin - highly positive expression in sarcomatoid tumor cells, as well as negatives of Vimentin areas with undifferentiated epithelial tumor cells; CK 5/6-Negative IHC expression and a barely noticeably positive reaction in single undifferentiated epithelial cells in a field with a large increase X100); CK7-highly positive expression in the epithelial cell component; CK AE1-AE3 highly positive expression in the epithelial cell component (Figure 2). Based on pathohistological morphology and immunohistochemical analysis, we determine the histological diagnosis-Biphasic malignant tumor/ combination of undifferentiated carcinoma with pleomorphic sarcoma or the so-called pulmonary sarcomatoid carcinoma.

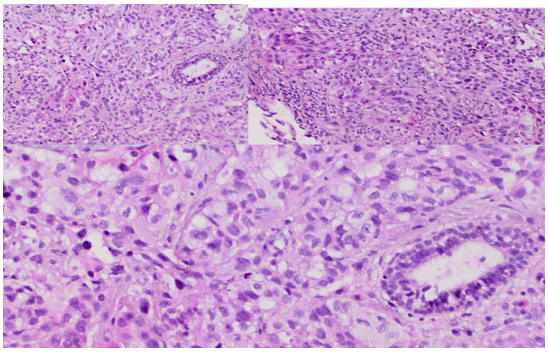

Figure 1: Photomicrography from a biopsy of a pulmonary tumor-Cellular variety involving cells of different sizes, as well as giant cells with whimsical multiple nuclei with atypical mythoses resembling tumor cells originating in muscle tissue, as well as cells with vacuoized nuclei, histiocyte like cells, atypical cells with hyperchomatic nuclei and bizarre tumor cells with foamy cytoplasm and pronounced atypical characteristic against the background of collagen stroma (H & E x 20, x40, x 400).

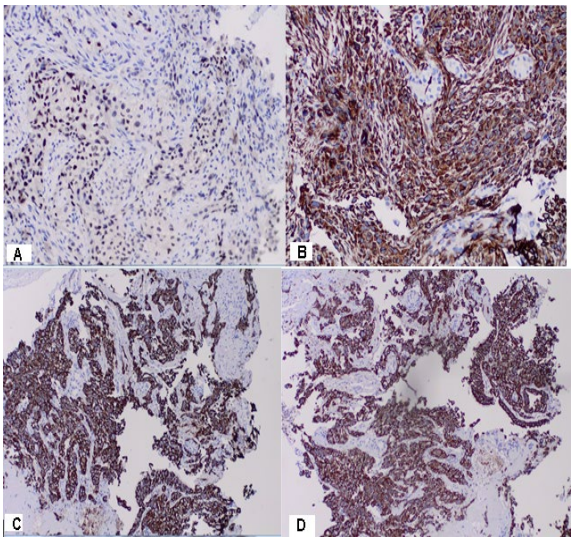

Figure 2: Immunohistochemistry from a biopsy of a pulmonary tumor-A) TFT1-focal positive IHC expression in epithelial tumor cells x20; B) Vimentin-highly positive expression in sarcomatoid tumor cells, as well as a negative Vimentin reaction in nests from undifferentiated epithelial cells x20; C) CK7-highly positive expression in the epithelial cell component x20; D) CK AE1-AE3-highly positive expression in the epithelial cell component x20.

Clinical Case No 2

Concerns a postmenopausal woman of 78 years with vaginal bleeding. An abrasio probatoria separata was performed, followed by a radical laparohysterectomy with lymphatic dissection. From the curettage material, after coloring with hematoxilin-eosin, fragments of malignant tumor with a solid structure are presented by compact neoplastic cells with oval atypical nuclei with high mitotic activity over twenty mitoses per field (Figure 3). Pathohistological examination of the surgical material-Uterus with athrophic endometrium. Myometrium no pathological changes; Left uterine tube-with fibrosis; Left ovary with albicious corporation and small inclusion cysts; Right uterine tube-no pathological changes; Right ovary with albician corporation and small inclusion cysts; A piece of soft tissues with blood vessels-no pathological changes; Uterine cervix a massive infiltration of a malignant tumor engaging the entire thickness of the smooth muscle layer, composed of two components one is an endometrial stromal sarcoma and the second nests from moderately low-differentiated squamous cell carcinoma with Keratin formation/ cancerous pearls (Figure 4 and Figure 5). IHC study of the surgery material from the uterine cervix after performed hysterectomy-Estrogen receptor, branch AP1-low positivity in the nuclei of the stromal endometroid sarcoma, as well as low positivity in the cells nuclei of the squamous cell carcinoma. Progesterone receptor, PGR636 branch-a negative reaction in endomethroid stromal sarcoma, slightly positive in squamous cell carcinoma. Cytokeratin, AE1,AE3 branch-highly positive cytoplasmic reaction in squamous cell carcinoma and negative in endomethroid stromal sarcoma (Figure 6A). SMA, branch 1A4-Diffuse positive reaction in the sarcomatoid component and negative in squamous cell carcinoma. The reaction is positive in the walls of the blood vessels and the smooth muscle layer of the uterine cervix (Figure 6B). The endometrial stromal sarcoma component is a CD10 positive (Figure 6C).

Conclusion: After morphological and IHC analysis of abrasion materials and subsequent surgical intervention (radical hysterectomy with bilateral adnexectomy and bilateral pelvic lymphatic dissection), the diagnosis of cervical malignant mixed Mullerian tumor composed of the endometroid stromal sarcoma and invasive squamous cell carcinoma has been made- TNM-pT1B pN0/G2-G3.

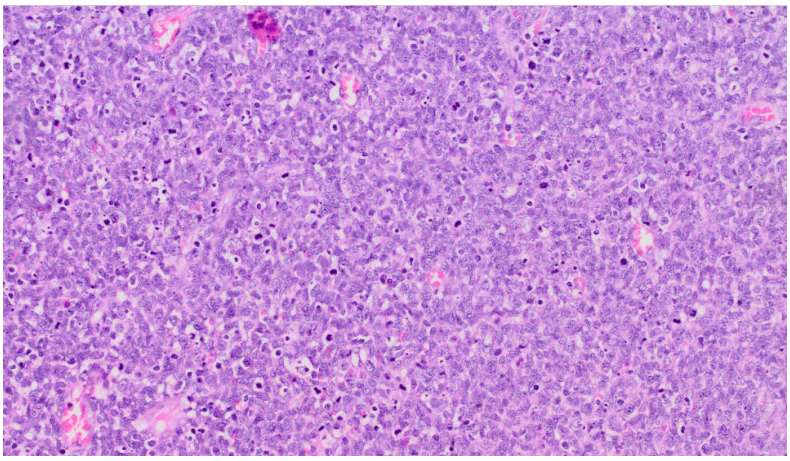

Figure 3: Photomicrography from a curettage material-Fragments of malignant tumor with a solid structure by compact neoplastic cells with oval atypical nuclei with high mitotic activity/H&E x20.

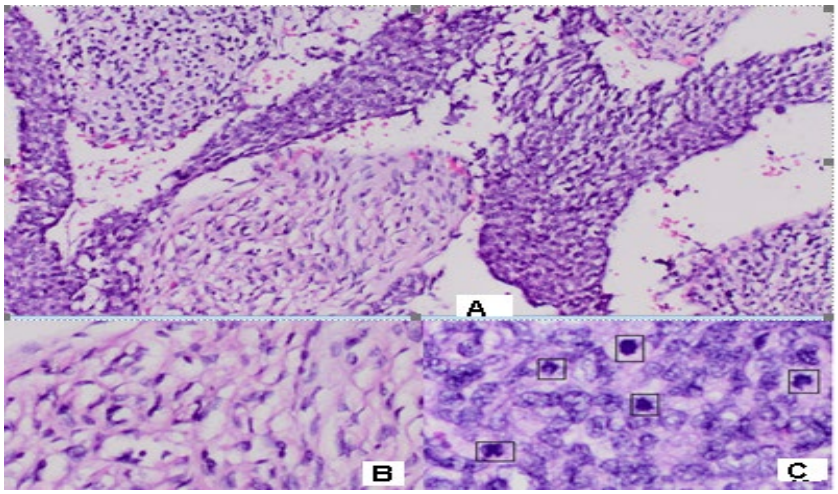

Figure 4: Photomicrography from cervical malignant mixed Mullerian tumor-A) Uterine cervix-A massive infiltration of a malignant tumor engaging the entire thickness of the smooth muscle layer, composed of two components- endomethroid stromal sarcoma and moderately to low-differentiated squamous cell carcinoma H&E x20; B) Endomethroid stromal sarcoma (sarcomatoid component) H&E x100; C) High mitotic activity of cells in the sarcomatoid component/over twenty mitoses per field (atypical mitoses are outlined with black rectangles) H&E x 400.

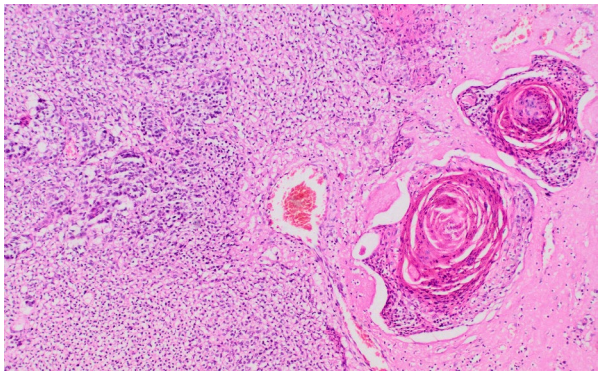

Figure 5: Photomicrography from cervical malignant mixed Mullerian tumor-Uterine cervix a massive infiltration of a malignant tumor engaging the entire thickness of the smooth muscle layer, composed of two components one is an endomethroid stromal stromal sarcoma and the second nests from moderately low-differentiated squamous cell carcinoma with Keratin formation/cancerous pearls/H&E x20.

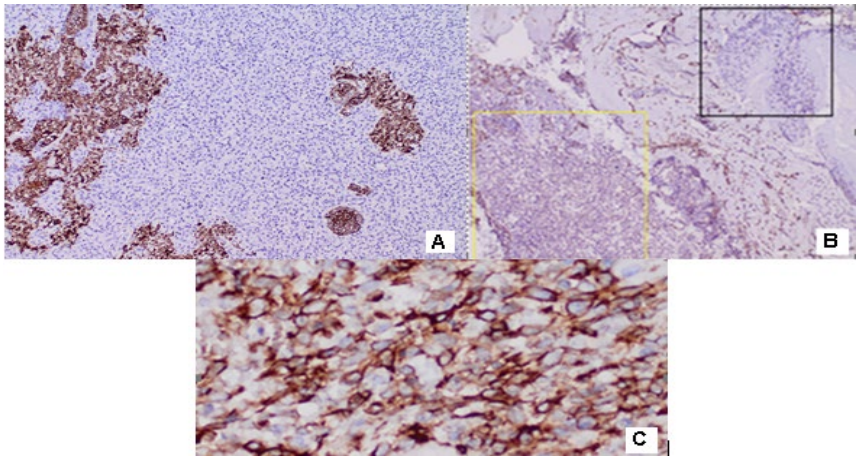

Figure 6: Immunohistochemistry from cervical malignant mixed Mullerian tumor. A) Cytokeratin, AE1/AE3 branch- highly positive cytoplasmic reaction in squamous cell carcinoma and negative in endomethroid stromal sarcoma x 40; B) SMA, branch 1A4-Diffuse positive reaction in the sarcomatoid component and negative in squamous cell carcinoma (shown with the yellow and black rectangle). The reaction is positive in the walls of the blood vessels and the smooth muscle layer of the cervix x 20; C) CD10 positive endometrial stromal sarcoma component x 100.

Clinical Case No 3

We present a 50 year-old woman diagnosed 7 years ago with invasive ductal carcinoma of the right breast/PT2 N1 M0; G2; estrogen and progesterone receptor status; Her2 status negative. In 2013 a Quadratectomy of the right breast with axillary lymphatic dissection was performed, followed by 6 courses of adjuvant chemotherapy (Ch) with docetaxel and postoperative radiotherapy (RT), ovarian suppression with LHRH agonist and antiestrogen hormone therapy with tamoxifen. Due to genital bleeding, a separated endometrial abrasion was carried out in July 2020. Pathochistological morphology and immunohistochemical analysis of a separated endometrial abrasion -Histological examination reveals a classic malignant bi-phasic cell growth with an undifferentiated epithelial component, composed of clear cells with relatively abundant cytoplasm and small nuclei. The cells form wide papillary areas and adenoid structures. Tumor infiltration is observed in the smooth muscle and in the sub-endocervical region. The epithelial component is surrounded by undifferentiated mesenchymal tissue, consisting of pleomorphic and bizarre tumor cells representing variable cell morphology of various sizes, as well as giant cells, usually whimsical with multilobulated nuclei, a large number of mitoses, histiocytic cells with vacuolized nuclei with an abundance of cystoplasm (sarcomatous component) (Figure 7, and Figure 8B). The carcinoma component takes into account a positive IHC reaction to Cytokerin, while in the sarcomatous cell component is negative. Both cell components are positive to Vimentin (Figure 8 and Figure 9). The same IHC expression is also observed in a metastatic inguinal lymph node (Figure 10). Based on morphological and immunohistochemical analysis, we have considered that it is a malignant mixed Mullerian tumor of the uterus.

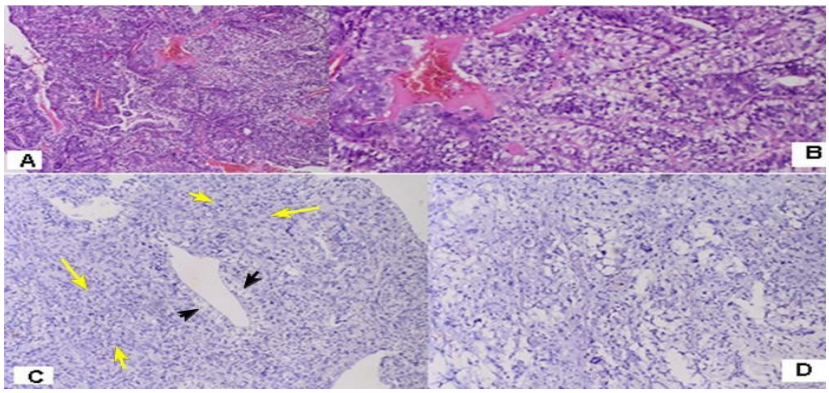

Figure 7: Photomicrography from uterine carcinosarcoma-A) Undifferentiated adenocarcinoma and sarcomatous cell component (H&E x 20); B) Undifferentiated epithelial component made up of clear cells with relatively abundant cytoplasm and small round nuclei (H&E x 40); C) Epithelial component, surrounded by undifferentiated mesenchymal tissue consisting of pleomorphic and bizarre tumor cells with variable cellularity and different sizes. Black arrows show the epithelial component, and yellow indicates the undifferentiated mesenchymal component (H & Ex40); D) The sarcomatous component with pleomorphic tumor cells, as well as giant cells, usually bizarre with multilobulated nuclei (H&E x 40).

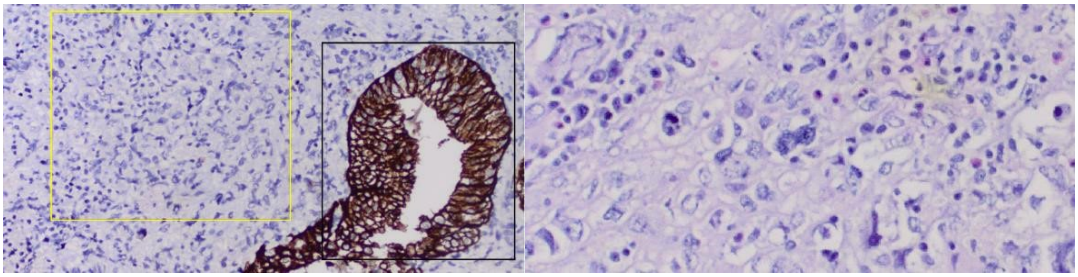

Figure 8: Photomicrography from uterine carcinosarcoma-A) Positive IHC reaction to Cytokeratin in the glandular carcinoma structures based on atypical glandular hyperplasia (limited by the black rectangle) and negative to Cytokeratin sarcomatous component with pleomorphic cells (limited by the yellow rectangle) x20; B) Saromatous cell component with pleomorphic and bizarre tumor cells with foamy cytoplasm and pronounced atypia, giant cells with multilobulated nuclei (H&E X200).

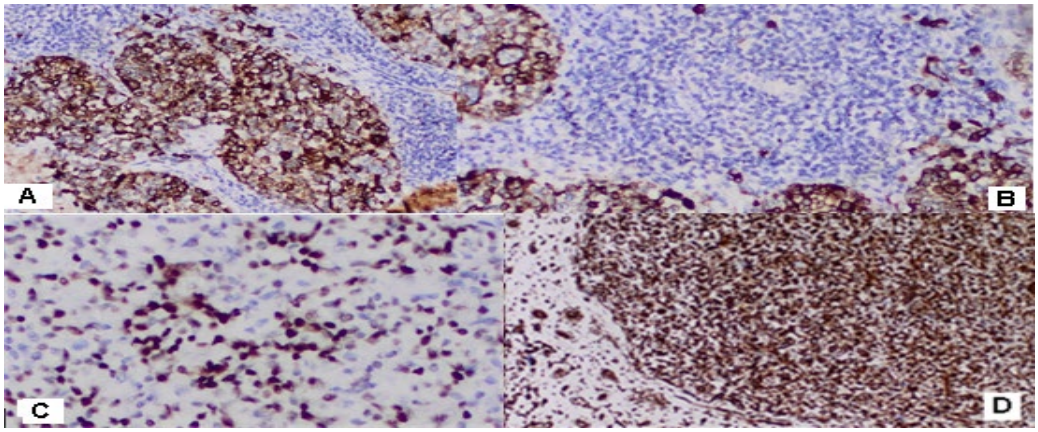

Figure 9: Immunohistochemistry from uterine carcinosarcoma-A) Positive diffuse reaction for Cytokeratin AE1-AE3 in the carcinoma component, which stands out clear cell adenocarcinoma x40; B) Negative reaction to Cytokeratin AE1-AE3 in the saromatous component, which is surrounded by the clear cell adenocarcinoma component x40; C) Positive reaction to the Estrogen receptor in the carcinoma component, the cells of which are arranged like chains x100; D) Positive for Vimentin sarcomatous component in endometrial carcinosarcoma x40.

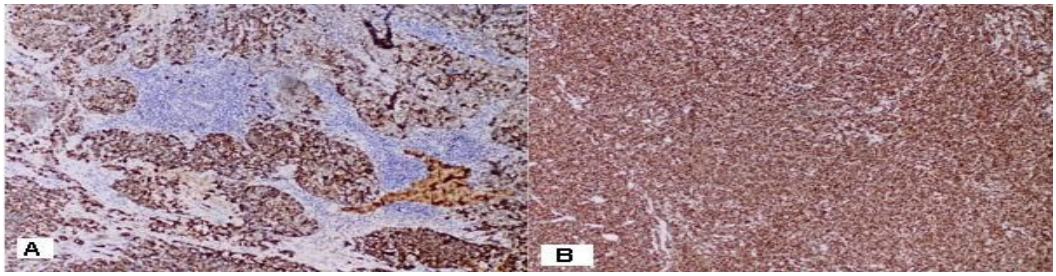

Figure 10: Immunohistochemistry of metastatic inguinal lymph node in uterine carcinosarcomaA) Diffuse positive IHC reaction to Cytokeratin AE1/AE3 in the carcinoma cell component, which highlights the clear cell adenocarcinoma and negative IHC expression to Cytokeratin AE1/AE3 in the sarcomatous component, mixed with adenocarcinoma cells x20; B) Diffuse positive IHC reaction to Vimentin; x20. Note-It should be remembered that there is a normal IHC expression to Vimentin in lymphocytes, neutrophils, macrophages and platelets.

Clinical Case No 4

We present a woman of 80 years with an extremely fast-growing thyroid tumor. CT data on pulmonary metastases. Histological result of a biopsy- Neoplasm with a high degree of malignancy characterized by spindle-shaped, polygonal and epitheloid cells with diffuse pleomorphism, without specific cellular differentiation. The morphological characteristic corresponds to an undifferentiated pleomorphic sarcoma (Figure 11/A, B). After a broad immunohistochemical analysis and reported positive expression for Vimentin, focal expression to SMA, high mitotic index and negative expression to Cytokeratin AE1/AE3, we diagnosed this neoplasm as a highly malignant undifferentiated thyroid sarcoma (Figure 12).

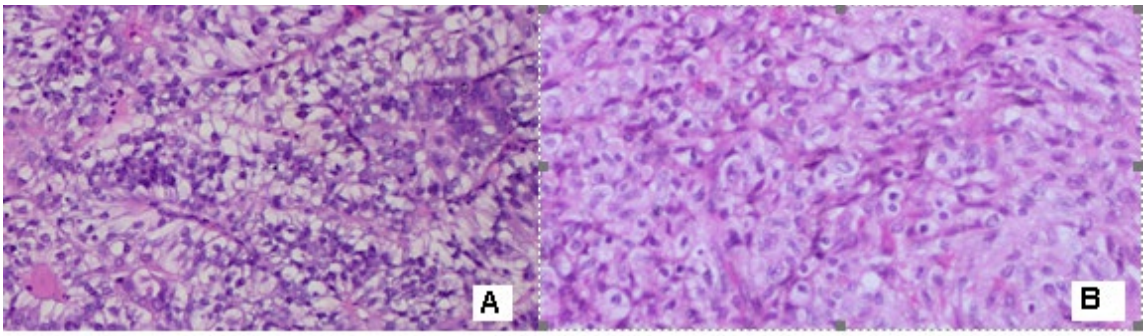

Figure 11: Pathochistological characteristics of undifferentiated pleomorphic sarcoma-A) Spindle-shaped, polygonal and epitheloid cells with diffuse pleomorphism, without specific cellular differentiation H&E X100;B) Based on collagenized stroma, a mixture of pleomorphic zones in the form of chains made of polygonal, spindle and epithelioid cells with hyperchrome nuclei, an abundance of eosinophilic cytoplasm, emphasized nuclear pleomorphism, necrosis zones, typical and atypical mitotic activity H&E X200.

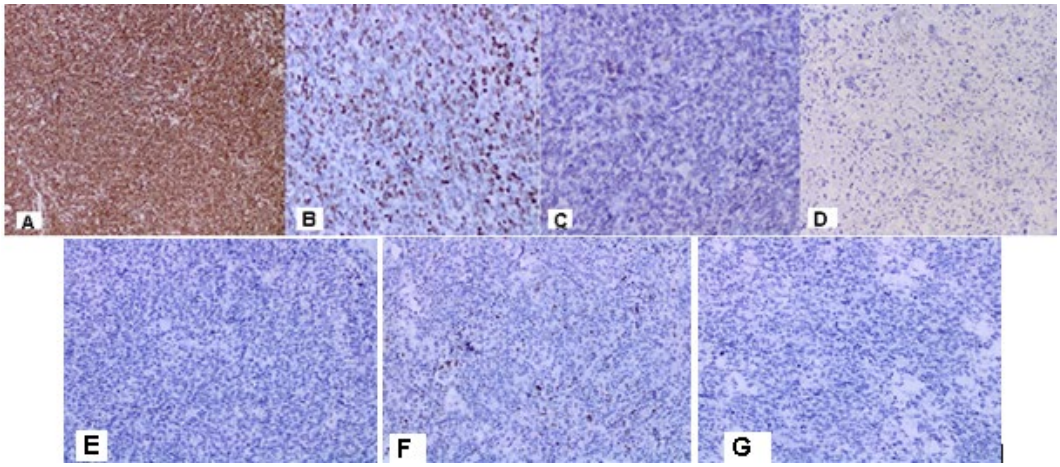

Figure 12: Immunohistochemical analysis-A) Vimentin- strong positive IHC expression in 100% of tumor cells x20; B) Ki 67-high mitotic index/50 mitoses per 10 HPF x20; C) Negative TTF1 expression x20; D) Negative Desmin expression x20; E) Negative Cytokeratin AE1/AE3 expression x 20; F) Focal positive expression to Smooth Muscle Actin (SMA) x20; G) S-100 Protein-Negative expression x 20.

Discussion

The sarcomatoid cell component in carcinosarmos can be homologous (nonspecific malignant stroma) or heterologous (malignant elements of a different tissue type, particularly cartilage) [2]. The Cancer Genome Atlas (TCGA) data supports the conversion and combination theories. Transcriptome and DNA methylome analyses confirm epithelial-mesenchymal transition as a mechanism of sarcoma differentiation [5]. There are four main theories regarding the histogenesis of uterine carcinosarcomas, namely: 1.The collision theory suggests that the carcinoma and sarcoma are two independent neoplasms; 2. The combination theory suggests that both components are derived from a single stem cell that undergoes divergent differentiation early in the evolution of the tumour; 3. The conversion theory suggests that the sarcomatous element derives from the carcinoma during the evolution of the tumour; 4. The composition theory suggests that the spindle cell component is a pseudosarcomatous stromal reaction to the presence of the carcinoma [6]. Immunohistochemical studies using antibodies against intermediate filaments, such as Cytokeratins (CK) and Vimentin, have shown that both the sarcomatous and carcinomatous components often coexpress CK and Vimentin [7-9]. Analyses of 1096 metastatic sites showed that carcinoma components tended to spread lymphatically, while sarcoma components tended to spread loco-regionally ($P<0.001$) [10]. Clinical, histopathological, immunohistochemical, ultrastructural, tissue culture, and molecular data confirm that the carcinomatous element is the "driving force" and that the sarcomatous component is derived from the carcinoma or from a stem cell that undergoes divergent differentiation [6]. The three clinical cases of carcinosaroma presented clearly show the two cellular components /epithelial and sarcomatous (Figure 2A-D, Figure 4A-C, Figure 5, Figure 7A-D, Figure 8B). In the fourth clinical case we present pleomorphic thyroid carcinosaroma, where the epithelial component is fully transformed into sarcomatous (Figure 11A,B). Intermediate filament (IF) proteins make up the largest family of cytoskeletal proteins in metazoans, and are traditionally known for their roles in fostering structural integrity in cells and tissues [11]. Vimentin is a 57 kDa type III IF protein

that is expressed mainly in mesenchymal cell types, including fibroblasts, bone-marrow-derived blood cells, and endothelial cells [12,13]. Most notably, in cancer, vimentin is most frequently used as a marker of mesenchymal cell types in epithelial-to-mesenchymal transition (EMT), a process that is critical to cancer metastasis [13,14]. At the first time, EMT has been defined by Elizabeth Hay in 1968, as a biological process in which epithelial cells can down-regulate epithelial characteristics and acquire mesenchymal characteristics [15]. EMT is a physiological event during embryogenesis (type I) but also happens during fibrosis (type II) and cancer metastasis (type III) [16]. Cells previously activated by the EMT programme often revert to the epithelial state; this mechanism is called mesenchymal–epithelial transition (MET) [17]. EMT is also implicated in the incorporation of tumor cells into blood and lymph vessels, commonly named circulating tumor cells (CTC). The presence of CTC has been associated with an increased risk of tumor recurrence and distant metastasis [18]. As the vast majority of cancer cells originate from epithelial cells, staining of IFs, most notably keratins, has proven to be a useful tool for pathologists to identify tumor and cell types [19,20]. EMT is characterized by the migration of epithelial cancer cells to invade the distant body sites by transforming into cells with the mesenchymal phenotype [21]. Overall, in the EMT process the expression and function of epithelial markers such as E-cadherin decline and mesenchymal markers like Vimentin increase [22]. The immunohistochemical expression for the epithelial markers/ Cytokeratin AE1/AE3, CK7 and E-Cadherin, as well as for the Vimentin and SMA mesenchymal markers, clearly distinguishes the two cellular components/epithelial and sarcomatous (Figure 2A,C, Figure 2A,C, Figure 8A, Figure 9, Figure 10). The saromatous component is made up of undifferentiated pleomorphic cells with a high mitotic index (Figure 3, Figure 4/C, Figure 6/B, Figure 7/D, Figure 8/B, Figure 9, Figure 11/B, Figure 12/B). The negative IHC expression for Cytokeratin AE1/AE3 and the highly positive for Vimentin in the 4th clinical case proves the completed EMT process of the epithelial cell component to sarcomatous (Figure 12A,E,F). Vimentin is upregulated in cells that have gone through the epithelial-to-mesenchymal transition, and it promotes invasion and migration via activation of Erk and Rac1 signaling pathways [11]. From the IHC analysis of material from a metastatic inguinal lymph node in uterine carcinosarcoma, we take into account a diffuse positive expression of Vimentin, which is an expression of its role in the metastatic process at EMT (Figure 10). The same IHC characteristics are observed in the metastatic cervical lymph nodes in the fourth clinical case with a pleomorphic thyroid sarcoma in whichin which the transdifferentiation from epithelial to sarcomatous cell component is completed (Figure 12A,F). Vimentin also seems to have a role in regulating stemness of cancer cells. Depleting vimentin expression through shRNA resulted in reduced population of breast cancer stem cells, as measured by high expression of aldehyde dehydrogenase [23]. Vimentin is consistently observed to be overexpressed during cancer metastasis and is therefore generally acknowledged as a canonical biomarker of type-3 EMT [24,25]. Among IFs, vimentin and nestin are positive regulators of cell migration and invasion [26], due in part to their roles in signaling events during EMT and stem cell.

Pro-tumorigenic IF proteins vimentin, nestin, and a subset of keratins, share a common trait in that all these proteins become induced upon wounding and tissue injury, when cells undergo hyper-proliferation [27]. Higher expression of vimentin has also been correlated with chemoresistance in various cancer types [28,29]. Multiple studies have shown that cancer stem cells display traits of cells that have undergone EMT [30]. Cancer cells may stably acquire one or more hybrid EM phenotypes expressing mixture of epithelial and mesenchymal traits. This multishaded EMT concept is known as epithelial-mesenchymal plasticity [31]. For many types of cancer, cancer stem cells (CSCs) represent a subpopulation with specific surface markers and functional properties including self-renewal capacity, long-term repopulation potential, and tumor initiation and progression capacity, which make these cells different from the bulk tumor cells [32,33]. The metastasis process involves the remodeling of the components of the EMT, the migration of tumor cells from the primary site into the surrounding stromal tissue, the intravasation through the blood and lymph vessels, and extravasation out from the capillaries [34]. In the sarcomatous component of uterine carcinosarcoma, pleomorphic tumor cells, bizarre atypical cells with foam cytoplasm, are observed, as well as giant cells with multilobulated nuclei (Figure 8B, Figure 9, Figure 10B). We believe that much of this cell component is represented by carcinoma stem cells, which are the main cause of distant hematogenous metastases of carcinosarcomas and pleomorphic sarcomas, as well as their pronounced radiotherapy and chemotherapy resistance (Figure 10A,B, Figure 11B, Figure 12A,E). CSCs are a small portion of cells within tumors and important research targets because of their tumorigenic potential and stemness properties [35]. Cancer stem cells (CSC) are known to resist therapeutic interventions and immune responses. Being pluripotent, these cells can provide cellular seeds to initiate new tumours at distant sites [36]. Cancer stem cells can exist in epithelial, mesenchymal or hybrid (mixed) states [16]. The epithelial-like state of CSCs is characterized by the downregulation of mesenchymal markers, such as vimentin, and the upregulation of epithelial markers, such as CDH1. The expression of these markers is reversed in the mesenchymal state of CSCs. Both epithelial and mesenchymal markers are expressed in hybrid state [37]. CSCs are found mainly in hypoxic niches, with low pH and with less nutrients [38], where they can initiate, maintain, and disseminate tumors [39]. Solid tumors are composed of heterogeneous cell populations including neoplastic cells, supporting vascular cells, inflammatory cells, and fibroblasts. Only the small subpopulation of CSCs is long-lived and has extensive self-renewal and tumorigenic capacities [40,41]. More and more studies suggest that cancer stem cells (CSCs) promote tumorigenesis, metastasis, recurrence and drug resistance as well as are the major source for heterogeneity of cancer cells [37]. The CSC model assumes that this subpopulation of cells sustains malignant growth, which suggests a hierarchical organization of tumors in which CSCs are on top and responsible for the generation of intratumoral heterogeneity [42]. Resistance of CSCs to radiation can be either intrinsic (or primary) or acquired, the

latter leads to the development of adaptive responses induced by the irradiation itself [43,44]. By the presence of a large amount of carcinoma stem cells in the saromatous cell component in carcinosarcomas (Figure 4C, Figure 6B, Figure 8A,B, Figure 9, Figure 10B, Figure 12A,B,E), we explain their exceptional radio- and chemotherapy resistance, as well as the high risk of distant hematogenous metastases.

Conclusion

Carcinosarcomas are rare extremely malignant neoplasms, composed of two cellular components/epithelial and sarcomatous. They are a classic example of epithelial to mesenchymal transition. To clearly distinguish between the two components, an immunohistochemical analysis is required to take into account the expression of Vimentin, which is most frequently used as a marker of mesenchymal cell types in epithelial to mesenchymal transition. By the presence of a large amount of carcinoma stem cells in the carcinosarcoma saromatous cell component, we explain their exceptional radio and chemotherapy resistance, as well as the high risk of distant hematogenous metastases.

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