Review Article

Genetic Insight into Malignant Mixed Mullerian Tumors, MMMT

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ABSTRACT

Malignant mixed Müllerian tumor, commonly called malignant mixed mesodermal tumor, MMMT and carcinosarcoma, is malignant neoplasms originate in the uterus, ovaries, fallopian tubes and other parts of the body which contains both carcinomatous (epithelial tissue) and sarcomatous (connective tissue) components. We reviewed whole-exome analyses of various tumours sequencing done from various sources to determine the mutational landscape of this tumour type. Alterations in genes with potential clinical utility are observed and included as PI3-kinase and homologous DNA repair pathways. This information gives us the significance of the dysregulation of chromatin remodelling in carcinosarcoma tumorigenesis and recommend new avenues for personalized therapy.

Keywords: Malignant mixed Mullerian tumors, MMMT, PTEN, ARID1A, PIK3R1, FIGO stage.

INTRODUCTION

Uterine carcinosarcoma (formerly called malignant mixed mullerian tumor) is a rare tumor of the gynecologic tract. It is classified as a mixed epithelial and mesenchymal tumor of the uterus in the 2003 World Health Organization classification[1]. It is higly difficult to distinguish carcinosarcoma from endometrial carcinoma or uterine sarcoma depending on clinical symptoms. The diagnosis requires histologic evaluation and genetic understanding. Histologically, carcinosarcoma tumors are poised of both carcinomatous and mesenchymal components, with homologous (composed of tissues normally found in the ovary) or heterologous (containing tissues which are not normally found in the ovary[2]. They are aggressive and have a poor overall survival rate. MMMT account for between two and five percent of all tumours resulting from the body of the uterus, and are establish largely in postmenopausal women with an average age of 60 years. Risk factors are comparable to those of adenocarcinoma uterus and include exogenous oestrogen therapies, obesity, and nulliparity[3]. The management principles of ovarian carcinosarcomas are the identical as those for epithelial ovarian cancer, but the proof for doing so is absent due to the little number of cases and need of randomized studies. This type of tumor usually shows an aggressive performance and poor diagnosis. Ovarian carcinosarcoma carry a particularly adverse prognosis. No effective chemotherapeutic regimen and radiotherapy exists for this types of tumors. Optimal cytoreductive surgical debulking is crucial and the FIGO stage is measured as the single prognostic factor[5]. Molecular studies point out that most neoplasms diagnosed as carcinosarcoma of the uterus is monoclonal, signifying that even though a minority may be true collision tumors/separate neoplasms, most represent a single neoplastic development. Based on molecular, epidemiologic, genetic, and histologic data, we can assume that most carcinosarcomas are essentially high-grade carcinomas with sarcomatous /stromal differentiation, similar to what is seen in other organ systems (e.g., metaplastic carcinoma of the breast, sarcomatoid renal cell carcinoma, spindle cell carcinoma of the larynx)[6]. Therefore, it may be more appropriate to refer to this lesion as sarcomatoid carcinoma of the uterus and possibly to submit to all of these neoplasms as sarcomatoid carcinomas of their respective organ systems[7-8]. The endometrioid carcinoma-like mutation profile got cluster of PTEN, ARID1A, PIK3R1 and POLE mutations, whereas the serous carcinoma-like mutation profile is having the clustering of TP53, PPP2R1A, EP300 and FBXW7 mutations[9]. Endometrial cancer is not a only disease but is composed of multiple dissimilar subtypes which have conflicting risk factors, precursor lesions, genetic changes, treatment options and clinical outcomes. Characteristically the subtypes include endometrioid, serous, clear cell, undifferentiated and mixed carcinomas (those composed of more than one subtype[10-11]. There are three theories for the origin of carcinosarcomas. The collision theory suggests that the tumours are biclonal arising from separate cells that later merge. The combination theory assumes that a common precursor differentiates bidirectionally and the conversion theory posits that a single cell undergoes metaplasmic differentiation. Molecular and histological proof ropes the conversion hypothesis and these tumours are now contemplation to derive from sarcomatous demarcation in a high-grade carcinoma[12].

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Surgical staging and deepness of myometrial incursion are the most important predictive factors. Its belligerence is

so important that, even if the disease is restricted in a polyp in the uterus, a lymphatic and blood vessels foray is found. Also stage I carcinosarcomas can frequently spread out, so lymph node metastases are identified in 14% of the cases[13]. currently it is widely accepted that , various molecular studies reporting comparable chromosomal aberrations, cytogenetic aspects, consistent failure of heterozygosis, matching p53 and K-ras mutations, and similar X inactivation pattern in both histological mechanism of the majority carcinosarcomas[14-15.]. In the *MSH6*-mutated belongings, C:G to T:A transition be the the largest part frequent, accounting for 53% of somatic mutations, but there was also an over illustration of C:G to A:T transversions (30%), probably as a consequence of the failure to repair mismatches arise as a result of oxidative injure. The phosphoinositide 3-kinase (PI3-kinase) pathways exaggerated by activate mutations in *PIK3CA* and *PTEN*. seeing that in endometrial tumours[17], mutations in *PIK3CA* and *PIK3R1* were commonly restricted, but loss of PTEN utility co-occurred with other genes in this pathway. Some tumours had *ARID1A* mutations and these were not experimental in the microsatellite-stable tumours of the uterus. a variety of *ARID1A*-mutated tumours also harbored frameshift and gibberish alterations in *ARID1B*. Alteration of the histone methyltransferase *MLL3* be identified in other cases of carcinosarcomas. *BAZ1A* is mutated at a short regularity in ovarian cancer and deletion of this gene be known to happen in renal papillary carcinoma[18]. Mutations in the tumour suppressor gene, *FBXW7*, recognized in a minute amount of cases. The preset protein is a member of the SCF (SKP-cullin-F-box) ubiquitin ligase complex that targets cyclin E for degradation[19].Tumour MM19 approved the earlier describe hotspot mutation, 505R>C. *FBXW7* is mutated in a number of diverse tumour types, including colorectal and haematopoietic malignancies, and has been lately reported in roughly a third of endometrial cancers[20]. The serine/threonine phosphatase, *PPP2R1A*, was mutated in one uterine carcinosarcomas. Alteration in this gene be originally recognized in ovarian clear cell carcinomas and more freshly in a series of tumour types, including a number of endometrial cancers and across special ovarian cancer subtypes[21].

DISCUSSION

MMMTs occur primarily in post-menopausal women among vaginal bleeding and uterine enlargement being the most frequent clinical presentation[22]. Normally, restricted metastasis to the vagina and pelvic cavity are recognized, but hematogenous broaden to the lung, liver, and bones is not unusual [23]. Exceptional cases have been report of MMMT metastasizing to the abdominal wall, skin and soft tissue, pancreas, thyroid gland [24]. The powerful prognostic factor is tumor stage follow by lymph node metastases, deep myometrial infiltration, participation of the cervix, and tumor size. The huge quantity extremely mutated genes, *ARID1A*, along with *ARID1B*, are key mechanism of the conserved, ATP-dependent SWI/SNF chromatin remodelling complex[25]. This composite use helicase association to permit transcription factor contact to DNA[26] and is central in the guideline of multiple cellular process, together with DNA repair, cell cycle development and cell migration[27]. Inactivation of the ARID1 complex appears to be predominantly significant in gynaecological cancers and in other tumours of the female genital tract[28]. In accumulation to mutations in *TP53* and *KRAS*, we understood and reviewed from various sources of literature that genetic alterations in chromatin remodelling genes, *ARID1A* and *ARID1B*, in histone methyltransferase *MLL3*, in histone deacetylase modifier *SPOP* and in chromatin assembly factor *BAZ1A*, in nearly two thirds of cases. Further review exposed somatic mutations in the mismatch repair genes, *MLH1* (MM20T) and *MSH6* (MM04T, MM12T and MM18T) in all cases, signifying that these defects were responsible for the observed mutator phenotype[29]. The huge accepted somatic alterations observed were single base substitutions, including non-synonymous coding changes, nonsense mutations and unite site alteration, by way of the outstanding mutations as small insertion and deletion. These mutations are reflection to arise as a result of deamination of 5-methyl cytosine at CpG sites and are a common characteristic across cancer types, as well as other gynaecological tumours.

CONCLUSION

This review clarify us vision to do rigid work at defining the downstream targets of chromatin regulators in carcinosarcomas as well as interventional clinical trials based on potentially actionable alteration pragmatic in cancer patients. alteration of the PI3K and DNA repair pathways have recognized precise actionable target, which have not been previously measured in this tumour type, as well as a common dysregulation of chromatin remodelling.

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