Journal of Cancer Management and Research
2023 Volume 1, Issue 1
DOI: 10.59657/2996-4563.brs.23.002

BioRes Scientia
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Research Article

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The Role of Maternal Microchimeric Cells in Cancer Development

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Abstract

Research question: Physiological or pathological roles of microchimeric cells (McCs) are not fully known and no definite information has been revealed yet. Revealing the histopathology of fetal-maternal microchimeric cells (F-MMcCs) may be an indicator of the future evolution of diseases, especially tumors, and may create new models.
Design: The presence of McCs in cancer tissue has been evaluated using FISH and cytogenetic techniques.
Results: We found 18% maternal microchimeric cells (MMcCs) in tumor tissue cells and 0.2% inperipheral blood cells of the patient with UPS. The frequency of these cells in tumor tissue was much higher than in blood tissue ($p<0.0001$).
Conclusion: Current findings reveal the current status and role of feto-maternal microchimerism (F-MMc) in cancer tissues and may provide a new perspective on Mc. Mc is a physiological phenomenon. However, microchimeric cells (McCs) can turn into pathology under unsuitable conditions and become a multistage part of the pathogenesis.

Keywords: microchimerism; fetal-maternal microchimeric cells; pleomorphic sarcoma

Introduction

Mc is the presence of small amounts of foreign cells in an individual's circulation or tissues. Mc can occur naturally and artificially in humans. The natural Mc is stem cell exchange between mother and fetus during pregnancy, which can lead to the existence of genetically unique cells that can persist for decades in both mother and child. This is the most common type of occurring human chimerism (Boddy et al, 2015). As a result of this; potentially Mc formation occurs in both mother and offspring. Thus, no one is born pure, so we are all born microchimeric (Mc). So, what are the physiological functions of these stem cells? The biological implications of McCs are still largely unexplored. Therefore, there are many unanswered questions about chimerism. It has been suggested to have pathogenic, beneficial and neutral roles for FMcCs (Galofré 2012). How these cells survive, how they adapt to the new environment, and how they acquire their ability to differentiate has not yet been explained. While their function is not yet known, it is crucial to functionally understand what McCs do in a normal healthy pregnancy and postpartum or offspring. Related to this, the clinical effects of MMcCs in organ repair, cancer development and treatment are only just beginning to be understood. In this study, we will try to explain the presence and potential effects of McCs in tumor tissues.

Materials and Methods

In this study, a 73-year-old male patient with a sarcoma who had an enlarging mass in his left breast was examined. There was no history of trauma and nipple discharge or other breast lumps. The patient had no history of breast cancer in the past. In addition, she had never received chemotherapy or radiotherapy and had no history of blood transfusions. The patient's breast ultrasound image showed a solid, hypoechoic mass with central necrosis in the left breast. The right breast and right armpit were normal. However, computed tomographic analysis revealed a 5x8cm mass with high peripheral vascularity and a hypodense necrotic center.

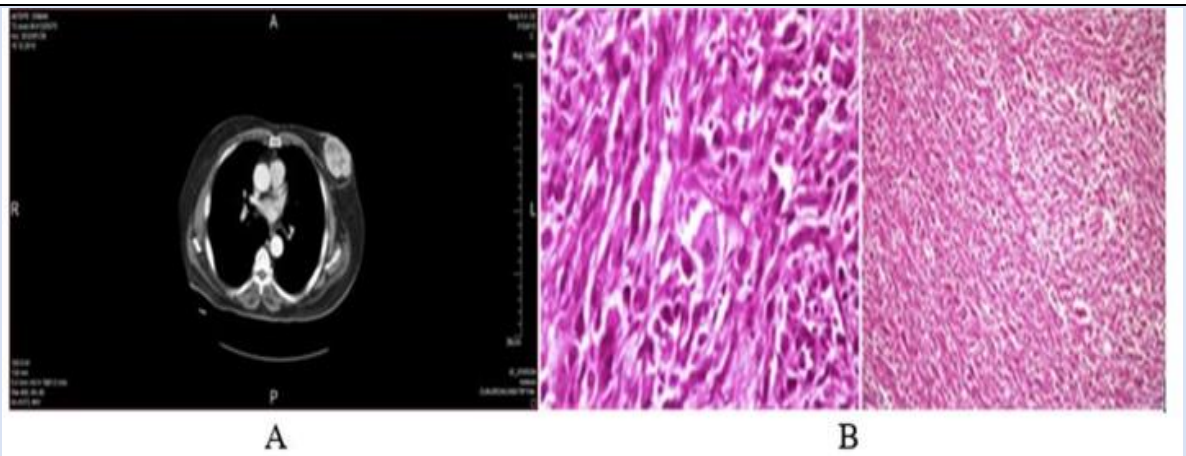

Figure A: A computed tomography scans of the mass: Normal bilateral axilla the tumour mass in the left breast with high peripheral vascularity and hypodense necrotic centre.
Figure B: pathological images of undifferentiated pleomorphic sarcoma

Fluorescence In Situ Hybridization (FISH)

Tissue samples of the primary tumor were taken by doctors in the general surgery department. Tumor tissue piece and 3-5 ml peripheral blood sample were taken for genetic studies. FISH and chromosome analyze of cancer and blood samples were performed in the genetics laboratory of Çukurova University, Faculty of Medicine, Department of Medical Biology. Tumor samples werecut into pieces mechanically and enzymatically dissociated with trypsin-EDTA (Biological Industries Israel Beit-Haemek Ltd.) for 1 hour. Standard cytogenetic techniques were used for interphase FISH. For this purpose, the method of Taştemir Korkmaz et al. was used (Taştemir Korkmaz et al, 2021). CEP X Spectrum Orange/Y Spectrum Green DNA Probe Kit (Abbott) was used to detect numerical abnormalities of X and Y chromosomes in tumor cells. A Y chromosome(green signal) and an X chromosome (red signal) signal were reported in the nuclei of male cells. Two X signals were found in cells of female origin.

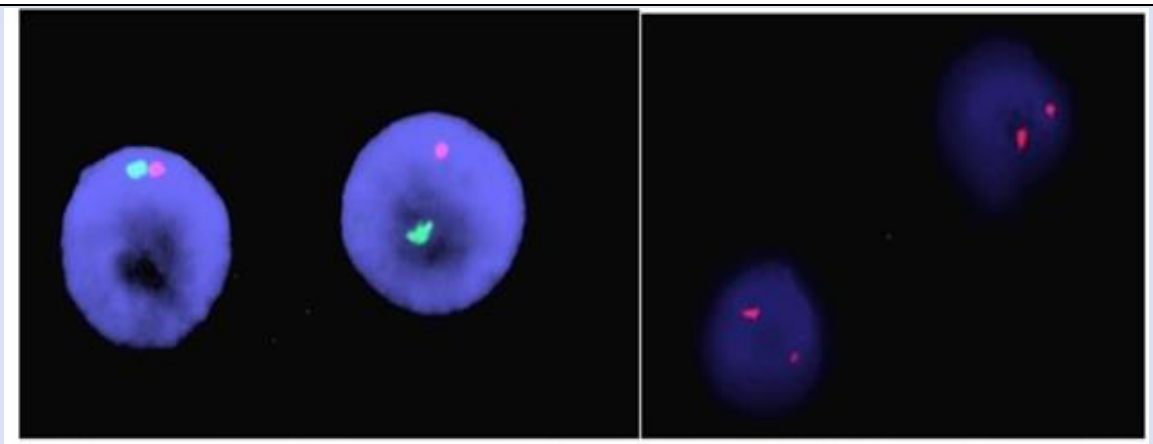

Figure 2: Copy number of chromosomes Y (green spots) and X (red spots) detected by fish in sarcoma cancer cells from a man case, two tumor nucleus showing XX chromosomes.

Approximately 500 interphase cells were analyzed using a BX51 Olympus fluorescence microscope equipped with Cytovision Probe Software (Applied Imaging, Santa Clara, CA).

Results

The findings indicating the presence of fetal and maternal cells in the blood or tissues of cancer patients are shown in Table 1. The presence of McCs in cancer patients has been evaluated using FISH and cytogenetic techniques. We found 18% MMcCs in tumor tissue cells and 0.2% in peripheral blood cells of the patient with UPS analyzed by FISH. The frequency of these cells in tumor tissue was much higher than in blood tissue ($p<0.0001$).

Table 1: Microchimeric cells in the blood and malignant tissue of the patient

Microchimeric cells (Number of cells with anomaly/total number of cells analyzed)(%)				
Case No	Age/Sex	Tumor type	Blood	Tissue
		Pleomorphic Sarcoma (PS)		
1	73/M	PS	1/528 (0.2%)	95/528 (18%)

Discussion

Today, we are only beginning to understand that McCs may play a role in becoming cancerous. Because there are so many unknowns about it. For example, it is still unknown whether Mc can be involved in the carcinogenetic process or whether fetal micr ochimeric cells (FMcCs) can differentiate into host tissues and participate in the maternal response to injury. Intense research has been carried out in recent years to clarify controversial reports and uncertainties on this subject. In the present study, our current findings and related literature are reviewed, trying to explain the relationship of McCs with cancer and their functions in tissues. In the present study, 18% of tumor tissue cells and 0.2% of peripheral blood tissue cells of patients with UPS were found to be composed of MMcCs. The frequency of these cells in tumor tissue was much higher than in blood tissue ($p<0.0001$). In addition, we have previously discovered maternal or fetal stem cells in the blood and cancer tissues of patients with lung (LC) and bladder (BC) cancers (Abat et al, 2014; Korkmaz et al, 2015). These findings draw attention to what the MMCs do in cancer tissue. At the same time, McCs were reported the cancer tissue of patients with BC. In addition, more McCs were found in cancer patients with high-grade BC, showing a correlation between the prevalence of these cells and the advanced stage of the tumor. Why are MMcCs so high, especially in sarcoma cancer tissue, andwhat is their role here? While these findings offer new perspectives on cancer biology, many questions remain about the role of Mc in cancer etiology and whether they are beneficial or harmful.As a result, the role of fetal cells in maternal health or disease has not yet been conclusively demonstrated. Unfortunately, we were unable to determine the nature of these MMcCs in the sarcoma cancer tissue, but their large number and large appearance of the tumors suggest that they are indeed tumor cells and not immune cells recruited to the tumor site. UPS is a well- known tumorin adults, usually involving soft tissues, and is a rare tumor that generally accounts for less than 1% of all cancers (Korkmaz et al, 2015; O'Donoghue et al, 2008). Although the cytogenetic backgroundof soft tissue sarcomas in humans is largely unknown, this is the first study to describe the role of Mc in the pathogenesis of UPS. The high proportion of MMcCs in UPS cancer tissue may be associated with the stroma of cancer. At the same time, the emergence of these cells in tumor tissuesmay be associated with their active participation in the complex tumorigenesis process involving tumor initiation and spread, including integration into the tumor stroma, facilitating neo- angiogenesis and metastasis, and inducing immune responses (Dubernard et al, 2008; Sawaya et al,2004; Gadi 2009; Nguyen et al, 2009). The participation of Mc mesenchymal progenitor cells couldresult in similar aggravation of prognosis. Similarly, lymph-angiogenesis has been associated with the occurrence of lymph-node metastases in melanomas (Dadras et al, 2005; Dadras et al, 2003). It has been suggested that the influence of FMcCs within the tumor is significantly associated with a higher number of fetal cells (FCs) in high-grade breast carcinomas. Larger-scale studies are neededto more clearly correlate the presence, number, and phenotype of McCs in the tumor and circulationwith tumor prognosis and evolution. A similar situation may be associated with LC and BC. Perhaps the microenvironment of normal lung cells may contribute to their propensity to develop tumors, as well as transforming McCs in the lung into cancer stem cells. These cells can transform into cancercells in the cancer microenvironment. A similar relationship has been reported between FCs within the cancer stroma in women with pregnancy-associated invasive breast cancer (Dubernard et al, 2008). Therefore, Mc may be a multistage part of the pathogenesis. Since FMcCs enter the mother's body via the placenta during pregnancy, they are frequently found in the blood and in the mother's lungs (Cirello 2010; Nelson 2009). However, it suggests an association with cancer, although FCsin the lung are probably only a byproduct of circulatory physiology. In one study, significantly moreFCs were reported in lung and thymus tissue, with a higher proportion of male DNA found in bonemarrow in the diseased lung compared to healthy bone marrow (Boddy et al, 2015; O'Donoghue et al, 2008).

Although the biological role of fetal cells is unclear, animal studies suggest that thesecells play a role in tissue repair rather than disease pathogenesis (Bianchi and Robert 2007; Khosrotehrani et al, 2007). Related to this, there is also evidence that FMcCs can participate in therepair of injured tissues. These cells are a particularly common condition that allows the persistenceof fetal progenitors that may host damaged maternal organs. It suggests that FMcCs could possibly contribute to maternal immune surveillance against tumors and thus play a cancer-preventing role. Indeed, fetal leukocytes aswell as epithelial cells or hepatocytes have been identified in differenttissues in women affectedby various immune and non-immune disorders (Dawel et al, 2007). Chemical hepatorenal injuries in rats have been reported to attract FCs to sites of injury (Wang et al,2004). Another study reported that FCs in the mother'sbrain doubled after birth as a result of neuraldamage (Tan et al, 2005). The protective role of FMc in suppressing tumor growth in pregnant women is best documented for breast cancer (Dhimolea et al, 2013). FCs are frequently found in the normal breast tissue of postpartum women. However, current research shows that the role of FCs inbreast diseases is complex. FCs were found less frequently in theblood and tissues of women with breast cancer compared to healthy controls (Jonsson et al, 2007; Potter and Schoeneman 1970; Brodsky et al, 1965). This suggeststhat excess FCs may actually be related to the mother's health.These cells were found to be significantly more prevalent in the peripheral blood of parous healthycontrols than in women who developed breast, thyroid, and several solid malignancies (Gadi et al,2008; Gilmore et al, 2008; Kamper-Jørgensen et al, 2012; Eun et al, 2013; Cirello et al, 2015).However, it has been reported that high-grade tumors in human breast cancers harbor significantlymore FCs than low-grade tumors, and FCs are also present in the tumor stroma (Dubernard et al, 2008; Dubernard et al, 2009). Thus, it is suggested that FMcCs may provide immune surveillance for breast cancer in women who have given birth. On the other hand, it has been shown that theprevalence of FMcCs is higher in the circulationof women who have given birth, and it has beensuggested that the absence of FMcCs in patientswith breast cancer may be a risk factor (Gilmore et al,2008; Gadi and Nelson 2007; Gadi et al, 2007). On the other hand, there is also evidence that fetalcells can participate in the repair of injured tissues.

The presence of FCs has been associated with both positive and negative effects on maternal health. Recently, many researchers have shown that cancer has the potential to be affected by McCs.It is thought that fetal mesenchymal progenitors and leukocytes may harbortumors after fetal progenitor cells are found in the inflammatory skin of the mother. The prevalence of McCs in cancer-affected patients was found to be significantly lower compared to healthy controls. It has been suggested that this may be due to increased clearance of FCs and specific uptake of FCs by an activated maternal immune system. FMc has been associated with some classical autoimmune diseases, but the role of these cells in normal health has not been defined. Following pregnancy, FCsmay cause a graft-host-like reaction in women, and the maternal immune response against these foreign cells may support an autoimmune reaction.A potential function of these cells may be in thesurveillance of malignant cells. To assess the presence and potential role of FCs in maternal cancers, the researchers examined maternal bloodor tumor tissue during or after pregnancy. The presence ofFMcCs was found in cervical tissuesobtained from patients with cervical cancer (Cha et al, 2003). Ithas been reported that the levels of FCs in lungand thyroid tumors of women with a history of pregnancy are much higher than in the surrounding healthy tissue (O'Donoghue et al, 2008; Cirello et al, 2008). Perhaps the micro-environment of stem cells in normal tissues may serve in a similar way to transform FCs in the lung into cancer stem cells. On the other hand, besides systemic sclerosis, a few other diseases have been associated with Mc. An alternative carcinogenetic role of FMcCs has been suggested in melanoma and colon cancer developing during pregnancy (Kamper-Jørgensen et al, 2012). Some researchers have therefore suggested that Mc is one partin multistep pathogenesis. Considering the potential of FMcCs to differentiate into different cells and their persistence in women after pregnancy, these cells may also act as cancer stem cells and cause tumors as a result of genetic changes or changes in their microenvironmental niches. This idea will open new avenues for understanding tumor biology and stroma formation.Our findings may also provide a new perspective on sarcoma, lung, and bladder cancers. It hasbeen recently thought that FMc may play arole in tumor development in women who have given birth.

However, the potential for FCs to develop into tumorigenesis-initiating cells in theinappropriate microenvironment, it seems plausible, but as yet unproven. At the same time, it suggests that FMcCs, which have also been identified in the supporting stroma tissue of the tumor, have deleterious roles. It is therefore possible that MMc might affect risk of some typesof cancer in women (and men). Just as it caused cancer in the breastarea in our male patient. Evidence has also been suggested for maternal cancer cells that form tumors in the fetus (Potter and Schoeneman 1970; Brodsky et al, 1965; Holland 1994). On the other hand, the findings suggest that FMcCs may play a role in breast physiology, but the effects on maternal health are not yet clear. However, there is anecdotal evidence that MMcmay be involved in the penetration of some hereditary cancer syndromes and may form tumorsin the fetus (Cha et al, 2003; Cirello et al, 2008). At some time, an association between FCs in cancer stroma and cancer has been reported in women with pregnancy-associated invasive breast cancer (Dubernard et al, 2009). All these findings and information point out that McCs may also play a role in the development of cancer. Now, can we say more comfortable now that F-MMcCs cause cancer?

Conclusion

Although FMc's role in normal health has not been fully defined, it has been associated with severalclassic autoimmune diseases and a small number of cancers. The presence of McCs in tumors, normal and healing tissues has led to the fact that while it may play a protective role in some cancers,it may play a triggering role in some other cancers. Our results suggest that the presence of McCs inUPS tissue may play a role in carcinogenesis, further revealing the potential relationship between Mc and disease. Thus, some researchers have suggested that Mc may be part of the multistep pathogenesis. Actually, Mc is a physiological phenomenon, but McCs can turn into pathology underunsuitable conditions. While McCs sometimes act as immune surveillance and help suppress tumorgrowth, they can sometimes act as cancer stroma and contribute to the growth of tumors. Distinguishing and detecting McCs will help us understand the role of Mc in health and disease. It may also be indicative of the future evolution of the tumor and establish models.

Acknowledgements: We thank the Doctors in Department of General Surgery, Department of Chest Diseases and Department of Urology, Faculty of Medicine, Çukurova University, Balcali- Adana, Turkey.

Informed Consent: It was obtained.

Author Contributions: Osman Demirhan: methodology, writing-review & editing, resources, project administration; Deniz Taştemir Korkmaz: project administration, review & editing; Nesrin Çetinel Şentürk: methodology.

Ethical Committee Approval: The study was approved by Local Ethics Committee of the Çukurova University, Faculty of Medicine (approval number: TF2009LTP45 project).

Conflict of Interest: The authors declare no financial competing interests.

Financial Disclosure: The authors declared that this study received no financial support.

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Cite this article: Osman Demirhan, Deniz Tastemir Korkmaz, Nesrin Cetine Senturk. (2023). The Role of Maternal Microchimeric Cells in Cancer Development, *Journal of Cancer Management and Research*, BRS Publishers. 1(1):1-7. DOI: 10.59657/2996-4563.brs.23.002

Article History: **Received:** March 31, 2023; **Accepted:** April 24, 2023; **Published:** April 28, 2023