

Opinion Article**Could Monocytes Colonized by Circulating Epithelial Cells of the Prostate Gland be a source of Metastasis of the Adenocarcinoma? A hypothesis based on a previous study****ABSTRACT**

Background: Recently we reported the successful in vitro cultivation of prostatic epithelial and stromal cells from patients with benign prostatic hyperplasia and adenocarcinoma of the prostate by liquid biopsy. In that study we noticed monocytes that were colonized by prostatic epithelial cells; this was confirmed using a monoclonal antibody to prostate epithelial cells. We also detected a deleterious effect exerted on the monocyte cytoplasm by a process yet to be determined.

Aim: To develop a hypothesis that will explain the significance of monocytes colonized by prostatic epithelial cells in the pathogenesis of prostate adenocarcinoma.

Study design: Retrospective analysis of images in the previous study.

Place and duration: Kilimanjaro Christian Medical University College, Tumaini University, Moshi, Tanzania. One month.

Results: We found that all monocytes viewed, without exception, contained intra-cytoplasmic prostatic epithelial cells and most of them presented with apparent cytopathology. The cytopathology presented as strand formation and shrinkage

of monocytes. Often the loss of integrity of monocyte cytoplasm could be arbitrarily graded as little to complete loss of cytoplasm.

Conclusion: We hypothesize that epithelial cells invade monocytes and colonize the cytoplasm. Monocytes colonized by epithelial cells then participate in the metastatic process of the prostate adenocarcinoma to different parts of the body. We report for the first time, a monocyte colonized by an epithelial cell of the prostate gland. This could also be an unrecognized phenomenon with other types of cancers.

Key words: “prostate epithelial cells”, monocytes, metastasis, colonization

1. INTRODUCTION

Macrophages are phagocytic cells that arise from the bone marrow promonocytes, which later differentiate into blood monocytes. When blood monocytes gain entry into tissues they settle and become macrophages. Phagocytic cells phagocytose foreign particulate matter which they may destroy through chemical processes including reactive oxygen or nitrogen intermediates. Monocytes infected by bacteria e.g. *Mycobacterium tuberculosis*, viruses, e.g. human immunodeficiency virus (HIV) and rickettsia e.g. *Anaplasma* (*Ehrlichia*) phagocytophylum, are killed by the respective pathogens. Monocytes can also be involved in adaptive immunity by presenting pathogen peptides to antigen presenting cells, which result in formation of antibodies and cytokines responsible for pathogen elimination. It is an immunological principle that monocytes, neutrophils and eosinophils ingest only foreign material or self material that has been modified enough to be recognized as foreign [1,2,3].

Macrophages can degrade the extracellular matrix upon which cancer cells are placed there by letting them loose to wander and migrate. Additionally, tumor-associated macrophages provide growth factors to cancer cells for their growth and division. The trade off is that cancer cells produce colony stimulating factor which stimulates the growth of the tumor associated macrophages [4].

2. MATERIALS AND METHODS

2.1 Retrospective examination of images in the previous study

We studied a total of 20 monocyte culture images from 34 patients afflicted with benign prostatic hyperplasia (BPH) and adenocarcinoma of the prostate (ACP). We chose the 3 most representative images that were clear enough to postulate our hypothesis in a publication. The images were stained by Giemsa stain, H&E stain and anti-androgen receptor monoclonal antibody. The following criteria were used for selection of the images: morphology included presence of nucleus, cytoplasm had integrity and there was presence of prostatic epithelial cells. Control images were monocytes cultured from young men who had no history of benign prostatic hyperplasia or adenocarcinoma.

3. RESULTS

Figure 1: Giemsa-stained 30-day old monocyte culture of a 22 year old participant. Note absence of intra-cytoplasmic epithelial cells in the monocyte cytoplasm. C=cytoplasm, arrows =nuclei; original magnification 40X.

Figure 2: Represents a 13-day old monocyte culture of an 80-year old patient exhibiting moderately differentiated adenocarcinoma, Gleason grade 10 and a plasma total PSA of 8.4ng/ml. Each of the 8 monocytes is overwhelmed by the

70 presence of intra-cytoplasmic epithelial cells appearing as dots in the image.
71 Prostate epithelial cells in monocytes were detected using a monoclonal antibody
72 to androgen receptor (see reference 2). Original magnification 40X.

73 Figure 3 shows 4 staged monocytes from a patient aged 70 years presenting with
74 a moderate to poorly differentiated adenocarcinoma, Gleason grade 9. Each
75 monocyte contains many epithelial cells in the cytoplasm. Cell 1 is considered an
76 invaded monocyte with little detectable effect in the cytoplasm. In cell 2 there is
77 an obvious loss of cytoplasm and strand formation. Cell 3 is a monocyte which is
78 smaller than the previous two but also loaded with prostatic epithelial cells.
79 Original magnification 40X.

81 **4. DISCUSSION**

82 The adoption of a monocyte cell culture technique to grow prostatic epithelial
83 cells derived from plasma of patients with benign prostatic hyperplasia and
84 adenocarcinoma has been described [1, 2]. The technique takes advantage of the
85 property of monocytes to stretch out their cytoplasm when grown in culture on
86 glass or plastic vessels [Fig. 1]. When this happens, it becomes possible to detect
87 microorganisms located in the cytoplasm after appropriate staining under light
88 microscopy.

89 It has been established that the main function of monocytes is the uptake of
90 foreign particulate organisms derived from exogenous sources e.g. bacteria or
91 protozoa. Cells that are specialized for this function are macrophages (in tissue)
92 monocytes, neutrophils and eosinophils (in blood). Therefore, macrophages and

monocytes recognize, engulf and internalize foreign exogenous organisms in their cytoplasm and where successful, destroy such invaders by different methods including use of oxygen or nitrogen intermediates [3, 4, 5].

Regarding monocytes as macrophage cells of the immune system, two authors will be considered. First, the concern whether tumor cells are recognized as foreign and the body would therefore mount an immune response in an attempt to eliminate the cancer much depends on the type of monocyte present at the site of the cancer. In this regard cancer has been discussed as an inflammatory process [6]. It was pointed out that the body may react differently to cancer depending on the type of monocyte that gets associated with the cancer. First, M1 macrophages can have a direct cytotoxicity on tumor cells whereas M2 macrophages can promote growth of tumor cells. Second, a question about where macrophages are found on the tumor and what functions they promote in the invasion. Some authors equate macrophages to 'traitor cells' because they are attracted to the tumor where they facilitate cancer cells to migrate out of the tumor, invade blood or lymph and therefore promote invasion. As if this was not enough, macrophages also provide growth factors to cancer cells for growth and division. The trade off is that cancer cells provide monocytes with colony stimulating factors for their growth [7]. Therefore the association between cancer cells and monocytes is mutually beneficial, to the detriment of the host. Finally, studies in the mouse inflammatory monocytes show that they may contribute to tumor development [8].

CONCLUSION

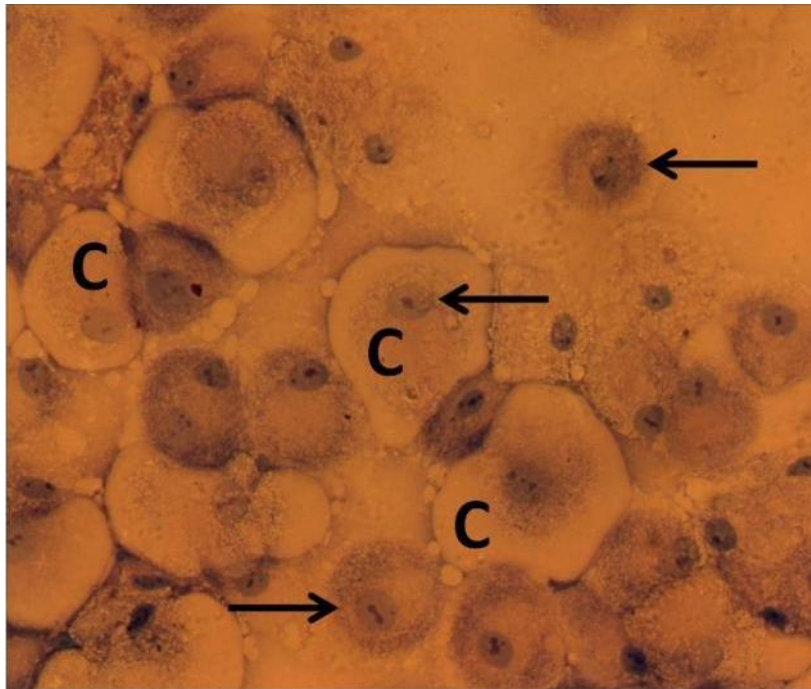
The analysis of images used in a previous study revealed important findings: First, all monocytes of the 34 patients in the study were colonized by prostatic epithelial cells. Second, there was apparent cytopathology of all the monocytes in the 34 patients. We were able to arbitrarily grade the cytopathology as to degree of loss of cytoplasm and cell size and apparent cell death in Figure 3. Third, literature search revealed that cancer is an inflammatory process and that some monocytes can promote cancer growth while others cause death of the cancer cells. Fourth, monocytes may be important cells for the metastasis of cells of prostate adenocarcinoma from the tumor to blood. Fifth, what was revealing and exciting, and probably the most important finding in this study, is that it has shown for the first time that prostate epithelial cells or cancer cells invade, colonize and kill other cells. This process is different from what is termed 'cancer invasion' i.e. migration of cancer cells through the tough tumor stroma and eventual arrival of the cells in blood or lymph. In this study we demonstrate invasion of epithelial cells into monocytes and their devastation of the monocytes they colonized. We conclude that monocytes could be conduits of cancer metastasis.

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172 **Figure 1:** Giemsa-stained 30-day old monocyte culture of a 22 year old
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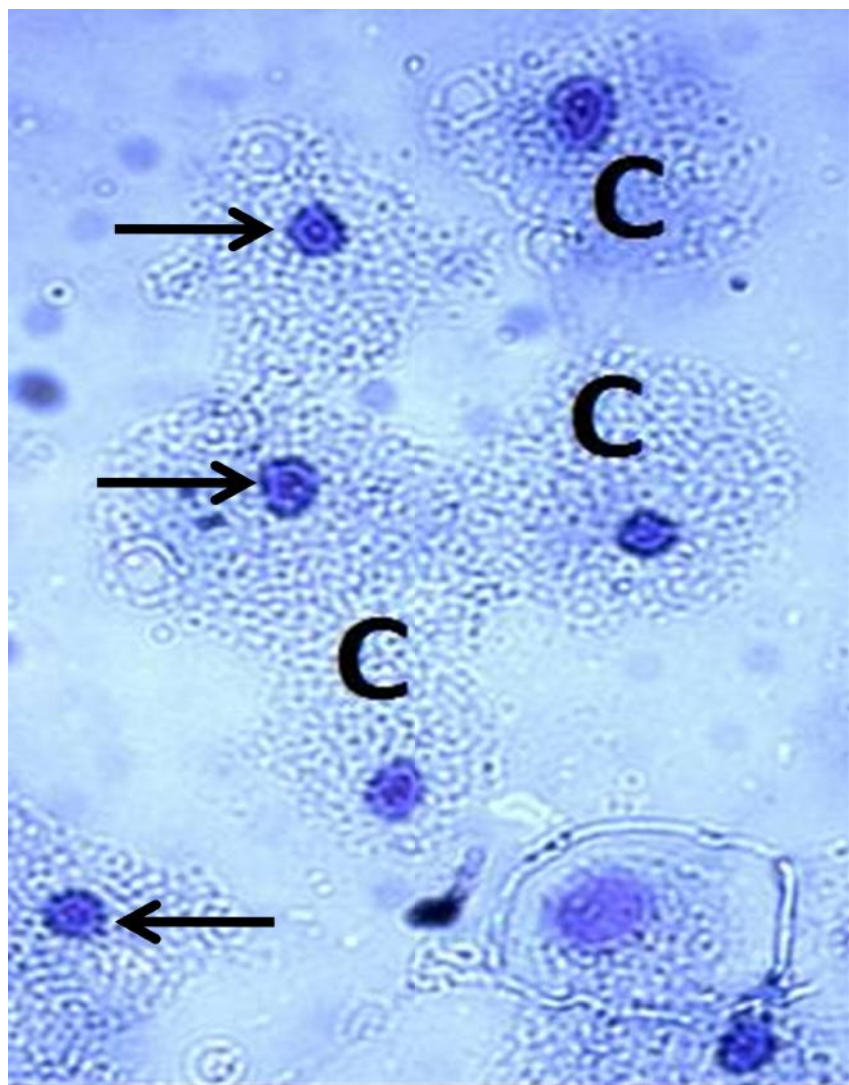
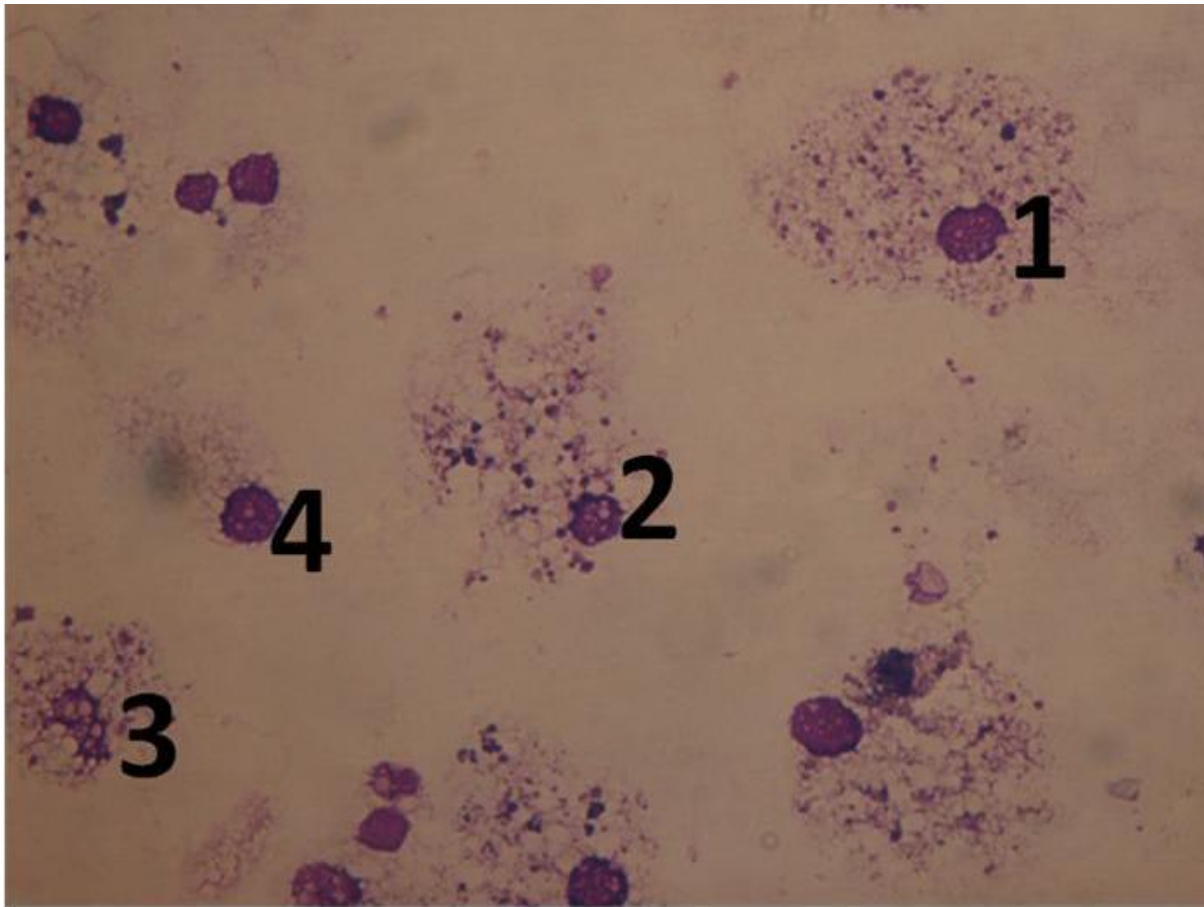


Figure 2: Represents a 13-day old monocyte culture of an 80-year old patient exhibiting moderately differentiated adenocarcinoma, Gleason grade 10 and a plasma total PSA of 8.4ng/ml.

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189 **Figure 3:** Monocytes from a patient aged 70 years presenting with a moderate to
190 poorly differentiated adenocarcinoma, Gleason grade 9. Original magnification
191 40X.