Significance of pigmented urothelial and non-urothelial cells in voided urine specimens: A case report and review

ABSTRACT

We present a case of metastatic malignant melanoma to the urinary bladder diagnosed on a voided urinary cytology specimen in a patient who visited the emergency department complaining of right flank pain, and dark urine. The patient reported having previous episodes of kidney stones. Additionally, more detailed clinical history obtained after the cytological diagnosis, revealed a previous excision of malignant melanoma on the back 10 years ago. The diagnosis of metastatic malignant melanoma was based solely on voided urine cytology. While metastases of malignant melanoma to urinary bladder are well known, the significance of pigmented cells in voided urine specimens is not well documented. In this article we provide a discussion as well as a review of the literature about possible disease entities associated with pigment containing urothelial as well as non-urothelial cells.

Key words: Hemosiderosis; melanoma; urothelial cells

Introduction

Of all melanomas, less than 30 cases of primary melanoma of the urinary bladder and urethra are reported in literature. Diagnostic features of melanoma of the urinary bladder include raised pigmented lesions, which histologically show spindled or epithelioid cells, with an abundance of necrosis, mitotic figures, and atypical melanocytes.

Case History

The patient was a 52-year-old male who presented to the emergency department complaining of dizziness, cough and right flank pain, and “dark” voided urine. Past medical history was significant for urolithiasis.

Based on urine cytological findings, the patient underwent a positron emission tomography–computed tomography (PET-CT), scan which revealed mild-to-moderate hypermetabolic hilar lymphadenopathy, suspicious for a metastatic disease.

Cystoscopy demonstrated multiple nodules, some ulcerated. In addition, more thorough anamnesis revealed that the patient had an excision of a melanoma on the upper back 10 years ago with no additional management.

Fresh urine aliquot was used to prepare slide smears. All slides were air dried and routinely stained with Papanicolaou stain using the standard laboratory protocols. The residual

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Cytological specimens were highly cellular and with high number of squamous and acute inflammatory cells as well as red blood cells [Figure 1a]. Urothelial cells and macrophages were also present. A separate population of cells with a plasmacytoid appearance and finely granular brown cytoplasmic pigmentation was identified. These cells had a small, round, eccentric nuclei, with no nuclear membrane irregularities, as well as preserved nuclear to cytoplasmic ratio [Figure 1b]. Immunohistochemical stain for S-100 with red chromogen is performed on cytospin material demonstrating nuclear and cytoplasmic positivity in the pigmented cells. These findings raised the possibility of malignant melanoma involving the urinary bladder. The bladder biopsy showed a submucosal malignant melanoma [Figure 1c] with a surface ulceration. The bone marrow biopsy demonstrated a trilineage hematopoiesis as well as numerous single pigmented cells consistent with metastatic malignant melanoma [Figure 1d].

Discussion

The diagnosis of malignant melanoma is established upon finding abnormal cells containing melanin pigment in their cytoplasm. For a cell to be labeled as malignant melanoma, the cytopathologist must be certain that the pigment is melanin, located in the cytoplasm and that the nucleus of the cell in question has a clear-cut stigmata of cancer.

We present a case of 52-year-old man with an unusual finding of pigmented cells in voided urine cytology. The dilemma for the cytologist is whether the cells observed in the urine are a cause for concern. In our experience, and as described in literature, pigmented cells in urine specimens are found to be relatively rare.[3]

The most frequent intracytoplasmic pigment is lipofuscin. This pigment is granular yellow-brown pigment granules and is considered to be “wear and tear” pigments usually found in the liver, kidney, heart, adrenals and nerve cells of the body.[4] Cytologically lipofuscin is rarely observed in urine specimens and is usually obscured by degenerative changes. The pigment is distributed mainly around the cell nucleus. Color and distribution features readily distinguished this pigment from melanin.

Hemosiderin pigment contains a complex mixture of proteins and iron. Histologically, it is as a coarse golden brown, pure brown, or black pigment that can be observed mainly in the cytoplasm of the reticuloendothelial cells (macrophages) or in rare cases, the urothelial mucosa.[5]

Melanin is a brown dusty intracytoplasmic pigment. It has been observed in benign conditions such as bladder melanosis, mucosal nevi, or metastatic melanoma.[6] It is not possible by cytological examination to determine the source of the melanin-containing cells. One important feature that is required to make such a determination is the cell discohesiveness leading to a higher cellularity in malignant cases when compared to benign cases. In addition, increased number of cells with a fine intracytoplasmic brown pigment in a background of hematuria raises the cytologists’ awareness and mandates a further investigation by cystoscopy. The diagnosis of malignant melanoma rests solely on tissue biopsy.

Urothelial hemosiderosis is a benign condition that results from the accumulation of hemosiderin in the bladder mucosa. This condition could develop from mucosal injury, blood transfusions, foreign bodies, or calculi. If cells containing hemosiderin are found in the urine, they may be mistaken for melanin-containing cells by an inexperienced cytopathologist, which may lead to an erroneous diagnosis of malignant melanoma. The difference is that these cells are not melanocytic in origin but reticuloendothelial. In one such case, the patient was a recipient of multiple blood transfusions.[7] The histologic examination reveals hemosiderin deposits in the lamina propria as well as numerous hemosiderin-laden macrophages and a normal urothelium. The hemosiderin pigment is a coarse brown pigment compared to melanin, which is a brown dusty inter-cytoplasmic pigment.

Urothelial melanosis is characterized by multifocal diffuse melanin pigmentation of the mucosa. Melanosis refers
to a condition of abnormal or excessive accumulation of melanin pigment in various tissues, most commonly skin and oral mucosa. This benign condition is found to be extremely rare with only a handful of cases described in literature.[9] When present, it is associated with hematuria or urinary incontinence, with both sexes affected equally. Cystoscopically, the lesion is flat, punctate, brown-to-black patches throughout the mucosa. Melanin granules are within the urothelial cells with or without bland-appearing mucosal melanocytes. These urothelial cells can present with cytological (reactive) atypia. When observed with atypia they pose a greater diagnostic challenge. Because we could not confirm the true benignity of the above stated condition by cytological examination only, a follow-up by cystoscopy with tissue biopsy was indicated.[9]

Cells originating from benign nevi may be indistinguishable cytologically from those of malignant melanoma. Even though the nevi are benign in nature, approximately 3–4% of all melanomas in the United States arise from them.[10] When these cells are observed in a urine sample, they may be indistinguishable from those of malignant melanoma. Such lesions must be excised to definitively determine their histology.

Primary malignant melanomas of the urinary bladder are very rare; however, metastases of malignant melanoma to the genitourinary tract are common. Malignant melanoma when observed in voided urine specimens is characterized by increased cell numbers, increased cell discohesiveness, with or without hematuria. To reach the diagnosis of malignant melanoma the cytologist must decide if the cells are melanocytic in origin or urothelial, as well as whether the cytoplasmic pigment is melanin, hemosiderin, or lipofuscin. In many cases, this determination may be difficult, especially in cases that are paucicellular, obscured by blood, or acute inflammatory cells. In such cases, a cellblock preparation from the residual urine is particularly helpful and provides a better sample for immunohistochemical analysis. If the cellblock preparation is insufficient, a diagnosis of “atypical pigmented cells” must be rendered with a note describing the cells that are observed with aforementioned differential diagnosis. A follow-up with cystoscopy and biopsy is recommended in such cases for proper diagnosis.

**Conclusion**

Pigmented cells observed in voided urine cytology specimens are an unusual finding. In majority of these cases, the underlying conditions are most likely to be benign, such as urothelial nevi, hemosiderosis, or urothelial melanosis, and in rare cases malignant melanoma. It is our recommendation that, if pigmented cells are observed in a voided urine specimen, a follow up cystoscopy is warranted.

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**Conflicts of interest**

There are no conflicts of interest.

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