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Malignant Melanoma in Genito-Urinary Tract

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1. Introduction

1.1 Adrenal melanoma

Adrenal melanoma- first reported by Kniseley et al in 1946 is a relatively aggressive tumor affecting the middle-aged adults.[1] The longest postoperative survival reported is 46 months.[2] In cases with adrenal metastases originating from a primary melanoma source, prognosis is worse with a median overall survival of 6 months.[3] Adrenal glands are the sixth most common site of distant metastases from melanoma (after lymph nodes (73.6%), lungs (71.3%), liver (58.3%), brain (54.6%) and bone (48.6%)).[4]

It manifests itself with flank pain and usually renal involvement is detected at the time of diagnosis. Additionally, distant lymph node metastasis could also be detected. Absence of previous unilateral adrenal gland involvement, presence of pigmented lesions without any signs of endocrine disorder, and negative immunohistochemical endocrine markers are typical characteristics of primary malignant melanoma of the adrenal gland. Presence of an occult primary lesion should also be excluded by autopsy.

Pluripotent neural crest cells are localized within adrenal gland medulla. They are precursors of melanocytes, neurons, glial cells of the peripheral nervous system, and adrenal chromaffin cells. Under the influence of microenvironment, and various growth factors, these multipotent cells might transform into different cell types.[5]

Differential diagnosis is difficult to establish based on the radiological criteria. Melanomas do not usually display disease- specific signs. Computerized tomography has been the preferred diagnostic tool for the evaluation of adrenal glands. Rajaratnam et al concluded that an adrenal mass greater than 5 cm in diameter, with central or irregular areas of necrosis/hemorrhage (and no lipomatous component) is a characteristic metastasic focus from malignant melanoma.[4] ^{18}F-FDG PET is a well-established diagnostic tool for restaging.[6]

Histopathologically, it is very hard to discriminate adrenal melanoma and pheochromocytoma. Melanin and melanin-like pigment can be detected in pheochromocytomas.[7] Some authors suggest that adrenal melanoma takes origin from pheochromocytoma, and thus it should be termed as melanotic malignant pheochromocytoma.[8] However, some others do not agree this opinion, and suggest that these tumors should have diverse origins.[9] Differential diagnosis between adrenal melanoma and pheochromocytoma could be established using immunohistochemical staining. Neuroendocrine markers including synaptophysin, chromographin and neuron-

specific enolase and neurosecretory granules (under electron microscopy) are detected only in pheochromocytomas.[2,9,10]

Since these tumors adhere to the adjacent kidney, nephroadrenelectomy is the preferred surgical treatment modality. Liatsikos et al performed the first laparoscopic adrenalectomy in a patient with primary adrenal malignant melanoma.[10] Because of its rare occurrence, a consensus has not yet been established with respect to adjuvant therapies such as radiotherapy[1] or chemotherapy with dacarbazine.[11] Adrenal metastases of melanoma provide additional evidence of systemic disease with an overall poor prognosis. For these patients, systemic therapy is usually preferred. Mittendorf et al suggested the option of adrenalectomy for those patients with no or limited extra-adrenal disease.[12]

1.2 Renal melanoma

Melanoma formed by melanin producing cells accounts for 68,000 newly reported cases, and is responsible for 8600 deaths annually in the United States.[13] It ranks sixth among the most frequently encountered malignancies in the UK, and malignant melanoma is most often encountered between the ages of 15 and 34 years.[14] Its incidence over the last decade has increased faster than the other types of malignancies.[15]

Renal metastasis of melanoma is rarely seen entity among the renal metastatic tumors. Accordingly, it is reported that kidney involvement in patients with malignant melanoma was around 24% to 50% of the cases.[16] In a series-consisting of 142 cases of metastatic genitourinary tract melanomas reported by Abeshouse, the primary cancer source was skin in 80 % of the cases.[17] However, renal involvement unrelated to any primary pigmented skin lesion was also reported.[18] Levin et al. reported a case of an isolated renal metastasis- 20 years after initial diagnosis and treatment secondary to an ocular melanoma occurring.[19]

Renal metastases secondary to cutaneous melanomas have been detected as multiple microscopic or millimetric foci. They usually progress insidiously and tend to invade adjacent perirenal space. They are highly vascularized. Boughan reported a metastatic case of melanoma localized in the upper renal pole and infiltrated the inferior vena cava (IVC).[18] Anecdotal reports of renal vein invasion by the tumor thrombi arising from secondary metastatic renal tumors have been encountered in the literature. Indeed, Klatte presented a case of renal metastasis of a malignant melanoma in which renal vein had been occluded by a tumor thrombus.[20] It was also underlined that renal metastases of malignant melanoma usually reflect end-stage renal disease.[20]

Transmission of donor malignancies to organ transplant recipients is a rare complication of transplantation. Malignant melanoma is one of the most commonly reported donor-derived malignancies. The mechanism of transmission of melanoma from the donor to recipient is unknown. Circulating tumor cells or dormant micro metastases residing in the organ parenchyma has been blamed for this transmisssion.[14] In the literature, there are 15 case-reports of melanoma transferred from donor organs to 28 recipients. The organs were transplanted in the range of six months to 16 years after the donors had undergone melanoma surgery.[21-24] MacKie et al had underlined that none of the patients with invasive melanoma should ever be an organ donor because of the possibility of the late and ultra-late recurrences in melanoma.[21] It has been estimated that between 0.98% to 6.7% of melanomas recur 10 years after the initial treatment.[25] Its ulcerated nature and depth of cutaneous infiltration are risk factors in favor of recurrences and also the distant recurrences were mostly encountered type of recurrence pattern (60%).[26]

Biological behavior of malignant melanoma is quite complex. Recurrences might be seen years after remission and it is believed that recurrences have been associated with re-activation of dormant cells. The maintenance of dormancy is hypothesized to be the result of a proficient immune system. Therefore, tumor cells remain dormant in an immunocompetent host. However immunosuppressed status of the patient as seen after transplantation serves as an ideal environment for the re-activation of the dormant cells.[27]

Radiological differentiation of renal metastases from renal cell carcinoma (RCC) is quite a complicated issue. The sensitivity of ^{18}F-FDG PET that is routinely used for the diagnosis of advanced disease, visceral, deep soft-tissue and lymph node involvement is quite low for the detection of early-stage malignant melanoma.[28] PET which uses a new analogue of fluoronicotinamide i.e. ^{18}F-MEL050 has a higher specificity, and sensitivity.[29] Definitive diagnosis of melanoma is established through cytological examination of the renal biopsy specimen. In malignant melanoma, cellular shapes and patterns might show variations depending of the originator tissue. Cytological features of a melanoma resemble those of the other poorly differentiated neoplasms like carcinomas, lymphomas, and sarcomas.[30] For diagnostic purposes immunocytochemical staining is used. In clinical practice, mostly S100 protein, and HMB-45 antibodies, and recently found MART-1 melanocyte antigens have been used.[30,31]

S100 protein is a calcium binding protein which had been isolated from brain tissue, and it is 90% sensitive for melanoma. However its sensitivity might drop to 70 % with respect to its discriminative potential between malignant melanomas, and spindle cell lesions with similar cytomorphologic features. In addition, primary renal tumors also stain with melanocytic markers. As previously demonstrated by Lin et al, 14.8 % of primary RCC's were stained positively with S100 protein.[32]

HMB-45 staining is relatively more specific for melanoma, and it is positive in 96.8 % of the cases. However its sensitivity decreases in spindle-cell and desmoplastic variants of melanomas, because of their lack of reactivity to HMB-45 staining. This phenomenon has led to the development of a more sensitive, and specific novel monoclonal antibody. MART-1 is a melanocytic antigen encoding gene which is only expressed in skin, retina, and melanocytic cells. MART-1 possesses 95 % sensitivity, and 97 % specificity for the detection of melanomas. However sensitivity of MART-1 reportedly decreases in the detection of spindle-cell, and desmoplastic variants of melanoma.

Angiomyolipomas originating from blood vessels, smooth muscle, and adipose tissue, and primary renal tumors carrying a translocation domain on t(6;11)(p21.1;q12) chromosome of TFEB ALPHA gene may also stain positively for melanin proteins. Epithelioid and spindle cell angiomyolipomas have a staining pattern for melanoma-specific, HMB-45 marker.[33] Translocation of ALPHA gene on chromosome on to intron 1 on TEFB located chromosome 6 is related to a RCC subgroup with pleomorphic histological characteristics, and they stain positively for melanocytic markers such as HMB-45, and Melan-A.[34]

Malignant melanoma is an immunologically active disease. Various forms of systemic immunotherapy such as Bacille Calmette Guerin (BCG), interferon-alpha and allogenic tumor vaccines have demonstrated significant improvements in overall and disease-free survival rates.[35-38] Currently, recommended treatment modalities for donor-related melanoma transmission consist of cessation of immunosuppressive therapy, achievement of rejection, and removal of the donor organ. In addition adjuvant chemotherapy or interferon-alpha therapy are also recommended to achieve complete resection of the tumoral mass.[21,39]

1.3 Malignant melanoma of the ureter

Ureteral malignant melanoma is a rarely seen entity. Generally it emerges as a metastatic focus. In the English medical literature limited numbers of ureteral malignant melanomas have been reported. Clinically, it manifests itself with symptoms of colicky pain. Radiologically, hydronephrosis, hydroureteonephrosis, and filling defects are seen in the upper urinary tract depending on the level of ureteral involvement. Ureteral mass lesion is verified by ureteroscopic examination.

Definitive diagnosis is established after immunohistochemical examination of the biopsy material. A clear-cut consensus on its management is lacking due to its rarity. Tumor can spread to all parts of the urinary tract after URS or DJ stenting. In their case-presentation, Gakis et al. proposed a management protocol for ureteral malignant melanoma in consideration of literature findings.[40-43] Accordingly, they recommended nephroureterectomy and regional lymphadenectomy for unilateral upper urinary tract involvement. Positive surgical margins, positive lymph nodes or depth of primary cutaneous tumor exceeding 1.5mm necessitate administration of adjuvant chemotherapy (dacarbazine). Local recurrences could be managed with resection and chemotherapy. In the presence of bilateral resectable lymphometastatic lesions, partial ureterectomy, and bilateral regional lymphadenectomy should be employed. Besides, adjuvant chemotherapy is recommended. For non-resectable lesions, radiation therapy and chemotherapy are among the treatment alternatives.

2. Malignant melanoma of the lower urinary tract

Lower urinary system contains bladder, urethra, and prostate gland in men. Symptoms of lower urinary tract diseases generally mimic each other. In older men, benign prostatic hyperplasia triggers symptoms such as dysuria, urgency, frequency, nocturia. On the other hand, over-active bladder is another frequently seen entity in women. Melanoma also mimics lower urinary tract symptoms during involvement of these areas.

2.1 Malignant melanoma of the bladder

Despite rarity of primary malignant melanoma of the bladder, genitourinary system metastases of the bladder melanoma have a relatively higher incidence. Renal (45 %), and vesical (18 %) metastases had been found in patients deceased because of melanoma.[44] Therefore, discrimination between primary and metastatic melanomas of the bladder is crucial. Stein[45] and Ainsworth[46] established some diagnostic criteria for primary bladder tumors: (1) absence of any previous skin lesion (2) or cutaneous malignant melanoma (3) or primary visceral malignant melanoma (4) recurrence pattern showing consistency with the primary tumor diagnosis (5) atypical melanocytes at the tumor margin on microscopic examination. In the literature including the most recent case- reported by Siroy AE et al. the number of cases with primary melanoma of the bladder amounts to 20.[44,47] However all the cases reported in the literature as primary melanoma of the bladder do not fit in these criteria of primary vesical melanoma.

Its initial clinical presentation is hematuria, as seen in other types of bladder carcinomas. However hematuria is a clinical sign of locally advanced disease.[1]Some patients present with lower urinary tract symptoms. During advanced stages of the disease, clinical symptoms peculiar to metastatic disease can be observed.

Cystoscopy is the primary diagnostic modality. Cystoscopy usually reveals a dark pigmented mass with varying dimensions. Mucosal layer surrounding the tumoral mass has a dark brown appearance, while the mucosa distant from the lesion has a pinkish white color.[46] Diagnosis is made with histopathological examination of the biopsy material. Immunohistochemical studies shorten and facilitate diagnostic work-up.

Despite treatment alternatives including transurethral resection, partial and radical cystectomy, radiotherapy, immunotherapy, and chemotherapy, overall it has a poor prognosis. Transurethral resection is curative for lesions restricted to epithelium, and actually the definitive cure could be achieved by radical cystectomy.[44,47] In cases where surgery is contraindicated or chemotherapy is not tolerated because of its side effects, radiation therapy and immunotherapy with interferon-alpha can be applied.[47] Despite all these treatment alternatives, the prognosis is poor and the patients are generally lost within 3 years because of metastatic complications.

2.2 Prostatic malignant melanoma

In general, prostatic melanoma symptomatically resembles benign prostatic hyperplasia. First, obstructive signs and symptoms are detected in these patients. Sometimes irritating symptoms might be more prominent and they may mimic urinary tract infections or overactive bladder. This symptomatic ambiguity may lead to misdiagnosis and delay correct therapy. Therefore, patients with refractory symptoms to treatments or improper features of patients for suspected diseases such as young patient with BPH symptoms must warn us to overlook another extraordinary disease.[48] Prostatic melanoma is a rare neoplasm of prostate and must be kept in mind in the differential diagnosis after a thorough evaluation. Rare incidence of primary prostatic malignant melanoma in clinical practice, early diagnosis and differentiation of primary malignant melanoma from epithelial cancer are extremely important considerations, because while prostate cancer can be treated as a chronic disease for years, malignant melanoma of the prostate can rapidly progress to terminal stage with a high mortality.[49-51]

If one suspects malignancy after digital rectal examination, computerized tomography and/or transrectal ultrasound as well as radical prostatectomy and if needed lymph node dissection should be added to the diagnostic work-up. Alternatively, transurethral resection or transrectal ultrasound guided prostate biopsy could be performed to establish a diagnosis. Notably, not only surgical approach but also chemotherapeutic treatment plays a major role in the management of prostatic melanoma.[48]

2.3 Urethral malignant melanoma

Primary malignant melanoma of urethra is a rare entity, representing less than 1% of all melanoma and 4% of urethral cancers.[52] Rarity and difficulty in diagnosis results in a fairly late detection and poor prognosis. Noteworthy, urethral malignant melanomas are generally associated with immuno-compromised conditions including alcoholism, dialysis, and poor self-care.

Patients with urethral malignant melanoma admit to the clinics with various complaints. Protruding mass is s one of the most common clinically observed because distal urethra is involved more frequently than the other parts.[53,54] Lower urinary system complaints sometimes mask melanoma mass-related symptoms particularly in males. Symptoms may

sometimes mimic benign prostatic hyperplasia or chronic prostatitis. Unfortunately, only after medical treatment fails in these patients, cancer diagnosis could be established with a significant delay.[55] Additionally, hematuria and urethral discharge are other complaints in patients with urethral melanoma.

Routine physical examination of urogenital system and inguinal region must be performed meticulously as well since a complete examination may sometimes provide crucial clues to reach final diagnosis. Direct visual detection of tumor mass in females is frequently easy and straightforward because of shorter length of female urethra. Likewise, most of the urethral tumor mass located in the distal part with protrusion could easily be detected.

Unfortunately, at the time of admission of the patients, there is no available specific serum tumor markers like- 5-S-cysteinyl-dopa, an intermediate metabolite of melanin biosynthesis which is used in postoperative melanoma follow-up, high in chronic renal failure- no urine tests or imaging methods to detect the exact nature of the lesion and neoplastic features in early period. After the diagnosis is verified, evaluation of recurrence, lymph node and other organ involvement must be investigated using ultrasound, computerized tomography, magnetic resonance imaging or PET scan.

Although atypical pigmented melanocytic cells might be seen in cytological examination, this clue should increase the suspicion of melanoma and lead to a more meticulous cancer work-up at this point. Unfortunately, cytology sometimes could not provide any evidence of cancer. However, even in cases of inconclusive cytology, false negativity must always be kept in mind. Histopathological examination of specimens is performed based on the cellular differentiation, pleomorphism, solidity and grade of tumor according to WHO's schema. Additionally, diagnosis is supported by immunostainings with a specific marker for melanoma (anti-Vimentin +, Protein S-100 +, HMB – 45 +, Melan A +; AE1/AE3 +, CD 20 +).

Although the optimum therapy has not yet been established, considering the rarity of the urethral melanoma, surgical intervention plays the major role in first line therapy. Melanoma spreads to the other organs via the lymphatic drainage. The urethra, particularly the distal urethra including fossa navicularis and urethral meatus are the most common locations and about 30% of patients already harbor metastasis at the time of diagnosis with dangerous boundaries with regards to the depth of invasion and size of the tumor mass.[57,58] While cancers of the anterior urethra preferentially infiltrate into superficial inguinal lymph nodes, those involving the posterior urethra generally infiltrate into pelvic lymphatic channels.[57] However, the presence or absence of lymph node metastasis is the most significant prognostic factor for survival, as survival rates are approximately halved by the presence of nodal metastasis. Consequently, melanoma's aggressiveness, higher stage, and palpable lymphadenopathy require lymphadenectomy. However, unnecessary lymphadenectomy may result in lymphedema, pain, infections and other complication. For this reason, lymphadenectomy must be standardized especially for those patients with:

1. Palpable adenopathy (extended lymphadenectomy superficial and deep inguinal LND)
2. Lesions more than 1 cm in size
3. Presence of ulceration
4. Clark's level IV-V

Modified lymphadenectomy must be performed for all anterior urethral lesions other than Tis.[59] Local relapses and systemic metastases frequently develop in the early postoperative period following the removal of primary urethral malignant melanoma. Therefore, surgery

alone is not adequate to control local relapses and systemic metastases, thus adequate postoperative adjuvant therapy is required to prevent the relapse and progression of the disease. Combined use of multiple chemotherapeutic agents such as cisplatin, dacarbazine, carmustine and tamoxifen has been recommended in lieu of monotherapy.[60] However; even combination regimens do not satisfactorily increase the survival rates of patients with metastatic melanoma. Immunotherapy based on α-interferon and tumor vaccines has also been suggested in recent studies.[61]

2.4 Penile, scrotal and testicular malignant melanoma

These organs are external organs of male genital system. Primary malignant melanoma of these organs will be presented together with the metastatic ones under the same title because of their close relation.

Penile melanomas usually present as pigmented macule, papule, or ulcerations with an irregular border; however, it might be unpigmented as well. It is typically found on the glans penis and less often on the prepuce. The American Joint Committee on Cancer system classifies cutaneous melanomas based on the depth of invasion (Clark staging) and tumor thickness (Breslow level, direct measurement). Hematogenous metastases occur through the vascular structures of the corporal bodies; and lymphatic spread to the regional lymphatic ilioinguinal nodes occurs by lymphatic flow.[62] Scrotal melanoma has also been detected with similar appearance of penile melanoma. Testicular, epididymis and seminal vesicle malignant melanomas are metastatic and display no symptoms until before reaching sizeable masses so as to be detected during physical examination, and are mostly detected at autopsies.[63]

Definitive diagnosis of penile, scrotal and testicular melanoma could only be established histopathologically. However, imaging methods such as CT or MRI may help to delineate the boundaries of the lesion and macroscopical invasion to neighboring structures. After treatment, nuclear scintigraphy is useful for whole body scanning. Starting from early 1990s- as an adjunct to follow-up scanning protocol, sentinel lymphadenectomy using radio colloid mapping and dye localization for melanoma has been described. This technique is minimally invasive and sensitive enough to detect the relevant nodes in the correct nodal location without complete dissection. When the sentinel node is negative for metastatic disease the incidence of micro metastases in the remaining structure is less than 1% to 2%.[64]

In patients with penile lesions less than 1.5 mm deep, less aggressive treatment with local excision has been effective.[65-67] However, the risk of metastasis to regional lymph nodes with a resultant poor outcome is high. Considering the rarity of the disease, aggressive treatment in selected patients with penectomy or partial penectomy of the primary tumor with bilateral lymph node dissection has been recommended.[65] Despite aggressive surgical treatment and chemotherapy, patients with metastatic disease have a poor prognosis.

Patients with penile melanoma of stage III or more have an extremely poor prognosis; the 5-year and 10-year survival rates of Japanese patients with stage IIIB melanoma are 40% and 38%, respectively.[68] Penile malignant melanoma patients with positive lymph nodes carry a poor prognosis of less than 2 years of mean survival.[65] According to the guidelines for treatment of patients in each stage, in addition to radical dissection of regional lymph nodes, DAV-Feron therapy is recommended as a postoperative adjuvant chemotherapy

for patients with stage III melanoma. 5DAV-Feron therapy dacarbazine, ACNU (nimustine hydrochloride), VCR (vincristine sulfate), plus interferon-b is recommended as a postoperative adjuvant therapy for patients with stage IIIB melanoma. Therapy can significantly improve the 5-year survival rate of patients with malignant melanoma compared to the DAV therapy alone.[69] The Feron therapy, in which interferon-b (300 ¥ 104 IU) is locally injected into the wound area for 10 days, is recommended as an adjuvant therapy for patients with stage I–II melanoma. Scrotal melanoma is treated with orchiectomy and lymphadenectomy; and additional chemotherapy must also be planned.[70]

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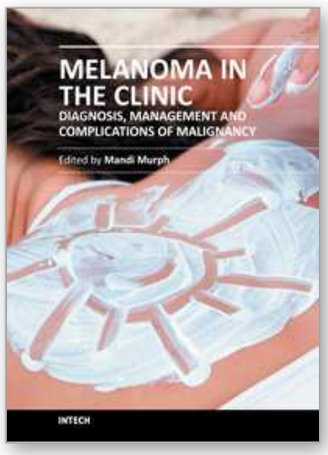

Melanoma in the Clinic - Diagnosis, Management and Complications of Malignancy

Edited by Prof. Mandi Murph

ISBN 978-953-307-571-6
Hard cover, 310 pages
Publisher InTech
Published online 23, August, 2011
Published in print edition August, 2011

This book provides an excellent overview of how melanoma is treated in the clinic. Since oncologists and clinicians across the globe contributed to this book, each area also explores the unique burdens that geographical areas experience from melanoma subtypes and how these are treated in different settings. It also includes several chapters that illustrate novel methods for diagnosing melanoma in the clinic using new technologies, which are likely to significantly improve outcomes. Several chapters cover surgical techniques and other present very rare or challenging clinical cases of melanoma and how these were treated. The book is geared towards informing clinicians and even patients how melanoma arises, what tools are available and which decisions need to be made by patients and their families in order to treat this devastating disease.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Abdulkadir Tepeler, Mehmet Remzi Erdem, Sinasi Yavuz Onol, Abdullah Armagan and Alpaslan Akbas (2011). Malignant Melanoma in Genito-Urinary Tract, Melanoma in the Clinic - Diagnosis, Management and Complications of Malignancy, Prof. Mandi Murph (Ed.), ISBN: 978-953-307-571-6, InTech, Available from: http://www.intechopen.com/books/melanoma-in-the-clinic-diagnosis-management-and-complications-of-malignancy/malignant-melanoma-in-genito-urinary-tract

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