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Merkel Cells and Merkel Cell Carcinoma of Genitourinary System Tumor with Aggressive Behavior and Poor Prognosis

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Abstract

Human Merkel cells (MCs) were first described by Friedrich S. Merkel in 1875 and named "Tastzellen" (touch cells). Merkel cells are primarily localized in the basal layer of the epidermis and concentrated in touch-sensitive areas. Their density varies among each anatomical site. Mostly they are concentrated in the palms of hands, predominantly in the finger pads, also in the soles and toes than in any other parts of the body. Concentration of MC in the external genitalia has not been studied, but some researchers detected some MCs in the male prepuce and in the female clitoris. Last year they were first described in the labia minora. Functionally they can be classified into some subpopulations with different functions: mechanoreceptive, endocrine, chemo sensitive. They belong to mechanoreceptors detecting tissue deformations and release various neurotransmitters to nerve endings. Tumor arising from Merkel cells called Merkel cell carcinoma (MCC). This highly aggressive malignancy occurs most often in the elderly white peoples on the skin of the head, neck and extremities. Its incidence is generally higher in men than in women. The rate of mortality is higher than in patients with melanoma and prognosis is rather poor. MCC of the genitourinary system are very rare, aggressive and may be misinterpreted with other cancers of genitourinary system. Most cases of MCC reported in the English literature in the women are in the vulva. In general MCC have an aggresive behavior, but those in the vulva are virulent with a 100% rate of inguinal node and also distant metastases. Prognosis of this carcinoma is very poor than prognosis of the MCC arising in other parts of the body.

Keywords: Merkel cells; Merkel-like cells; Merkel cell carcinoma; MCC; Female genitalia

Introduction

Merkel cells

Merkel cells (MCs) (Figure 1a and 1b) are post-mitotic, neuroendocrine cells found in the epidermis of vertebrates [1,2]. They named according the German anatomist and histopathologic Friedrich Sigmund Merkel in 1875 (Figure 2) who first described these interesting cells. They were referred to as "Tastzellen" or "touch cells." [3]. In the glabrous skin they formed clusters connected with nerve endings and named as "touch corpuscles" (Tastscheiben) [3]. The human and animal MCs have been a subject of investigation in many studies for over a century, but their distribution, function and origin still remain unclear [4]. These rare cells are found in the basal layer of the epidermis and grouped in touch-sensitive locations in glabrous and hairy skin and in some mucosa [2]. Their density varies among each anatomical sites [5,6]. Mostly they are concentrated in the palms of hands, predominantly in the finger pads, also in the soles and toes than in any other parts of the body [7]. They are also present in the lips, hard palate, gingiva [4], oesophagus [8], and human eyelid [9]. Concentration of MCs in the external genitalia has not been studied, but Cold and Taylor [10] detected some MCs in the male prepuce and in the female clitoris. Last year Schober et al. [11] first described MCs in the labia minora. There is no occurrence information about the MCs in the vagina. The regions richer in MCs are involved in tactile perception, underlining the sensory receptor function of MCs [12]. Functionally, they are in close contact with nerve fiber endings to form a synapse-like contact zone and receive all environmental stimuli [11]. Some MCs are not associated with nerve axons [13]. Characteristic features of MCs are: oval shape, size about 10-15 μm in diameter, large, pale, lobulated nucleus, spike-like cytoplasmic projections called „microvilli" which interdigitate with adjacent keratinocytes [14]. They are attached to the neighbouring keratinocytes by relatively few; small desmosomes located on the cell body and occasionally on the dendritic-like processes [15]. Ultrasturcturally, they have dense-core secretory granules in the cytoplasm near the nerve fiber connection [15]. Visualisation of MCs in routine light microscopy is not possible, therefore we need special technique for their identification [16,17]. Antibodies against simple-epithelial cytokeratines, especially anti CK type 20 provide the highest degree of specificity and give an easy identification of MCs at the light microscopic level [17]. Other identification method in light microscopy is based on incorporation of fluorescence FM-dyes [water-soluble, lipophilic, styryl, nontoxic dyes] into living MCs. [18]. The uranaffin reaction has been used in electron microscopy, to detect mammalian intraepithelial MCs [19]. Uranaffin reaction was introduced as an ultrastructural stain for the localization of adenine nucleotide in organelles storing biogenic amines [19]. According Lucarz and Brand [15], functionally they can be classified into some subpopulations with different functions: mechanoreceptive, endocrine, chemosensitive. They belongs to mechanoreceptors detecting tissue deformations and release various neurotransmitters to nerve endings [15,20]. Thanks to dense-core granules in the cytoplasm they were considered to be cells of APUD system [group of cells with endocrine functions] [15]. According some scientist [21,22], they may play role in the proliferation and differentiation of the keratinocytes. Presumptive functions of Merkel a cell summarize (Figure 3).

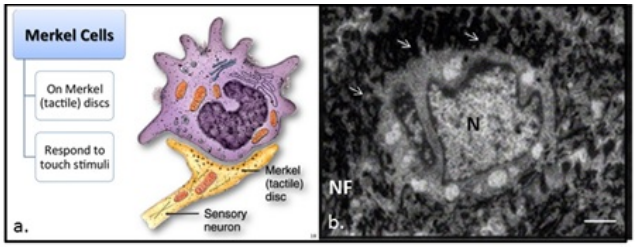

Figure 1: (a) Schematic picture of Merkel cell [23]. (b) Electronogram of Merkel cell from the human skin. Ultrastructure of MC- pale, lobulated nucleus (n) and "spine-like" processes (microvilli) with variable lenght (arrows), NF- nerve fiber. Human skin from abdomen. Bar 2 μm.

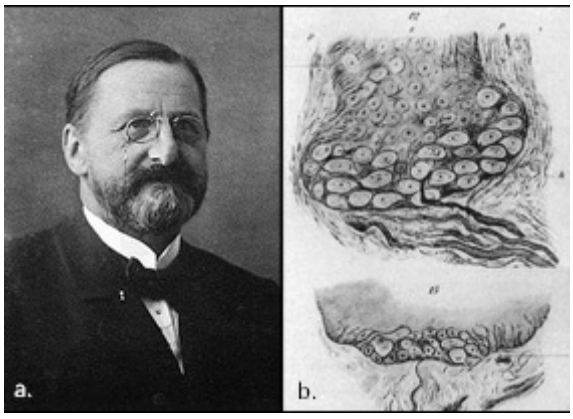

Figure 2: Fridrich Sigmund Merkel (1845-1919) (a) and his original drawings of Merkel cells (b) illustrating touch corpuscles in different mammals. Each corpuscle consists of Merkel cells connected to nerve terminals [3].

Merkel cell carcinoma [MCC]

This rare neuroendocrine, cutaneous neoplasm was first documented and described by Toker in 1972 [24]. Typical predilection sites are sun-exposed skin regions e.g. head, neck and extremities of elderly persons. [25-27]. This highly aggressive malignancy occures most often in the white population [28,29]. The incidence of MCC is generally higher in men than in women. Risk group includes the elderly people with immunosuppression from organ transplant and HIV infection [27,30]. MCC presents as a firm, painless, red- violet, rapidly enlarging, cutaneous nodule (Figure 4) [25,27,31]. Ethiology of MCC is linked to the presence of clonally integrated Merkel cell polyomavirus (MCPyV) and/or mutagenesis from ultraviolet [UV] light exposure [32]. Histologically, the tumor commonly involves the full thickness of the dermis (Figure 5) and frequently extends into the subcutaneous fat and adjacent skeletal muscle [33]. Histologically, MCC has been classified into three distinct subtypes: trabecular, intermediate, small-cell type [33]. Diagnosis is based on typical histology representation on haematoxylin-eosin stained slides together with the results of immunohistochemistry [34].

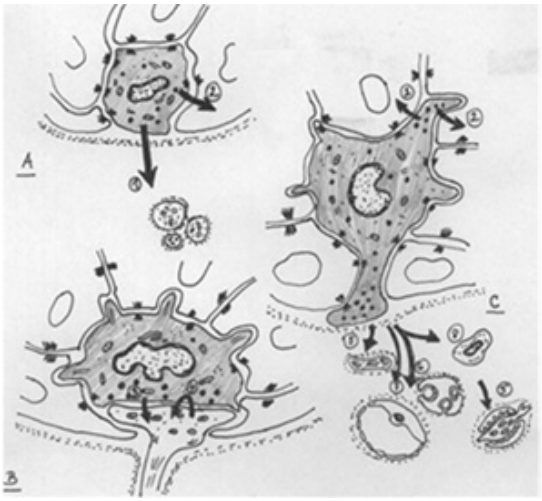

Figure 3: Schematic summary of presumptive subpopulations and functions of Merkel cells [16]. (A) During the early development of integument, trophic or stimulative substances may be released from the MCs to growing nerve fibers [1] and keratinocytes [2]. (B) In the Merkel cell-neurite complex, the MCs may release neurotransmitters or neurotrophic factors [3] or neuromodulators [4] to the sensory nerve terminal. (C) The non-innervated MCs in the fully developed skin may act to support normal keratinocyte differentiation [2] or normal actions of nervous structures [5,6]. The cell may also release substances to blood vessels [7] or cells of connective tissue [8].

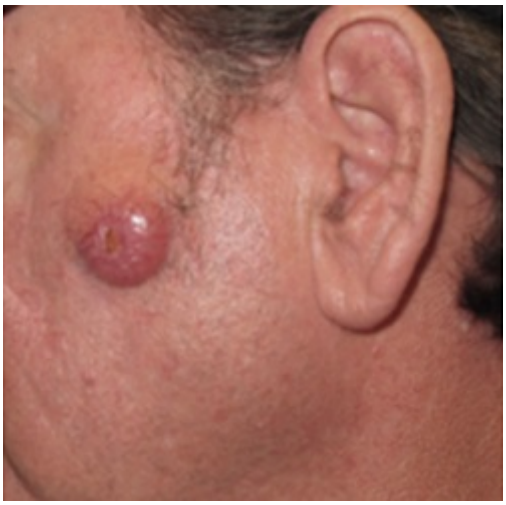

Figure 4: MCC arising on the left cheek of a patient with chronic immune suppression [31].

CK-20 is specific, highly sensitive marker for MCC [positive in 89 to 100% of cases [35]. Mortality of the cancer is estimated to be between 33% and 46% [27,36] and the rate of mortality is higher than in patients with melanoma [27,37]. MCC is the second most common cause of death after melanoma [37,38]. Metastasis most commonly involved regional lymph nodes, followed by distant lung, skin, CNS,

liver and bone [39]. The prognosis is rather poor. According by Kokoska [40] and Linjawi [41] the 2-year survival rate is 30%-50% in the patients of theirs study. Treatment, of MCC requires wide excision of the primary tumor, surgical biopsy of the draining lymph node bed, and adjuvant radiation therapy to the tumor bed and draining nodal basin [33]. Although the tumor is chemoterapy-sensitive, the role of chemotherapy is discutable, because responses to chemoterapy are seldom durable.

Merkel cell carcinoma [MCC] in the organs of genitourinary system

Primary MCCs of the genitourinary system are very rare, aggressive and may be misinterpreted with other cancers of genitourinary system. MCC of genitourinary tract occur in the patients aged between 30-80 years [42]. In the male genitourinary system, Best [43] reported case of MCC in the scrotum and Tomics [44] in the penis. Most cases of MCC reported in the English literature in the women are in the vulva (Table 1) [42].

References	Age (y)	Location	Size (cm)
Tang et al., 1982 [45]	67	labium minus	1,5
Bottles et al., 1984 [46]	73	labium minus	3 × 2
Copeland et al., 1985 [47]	59	labium minus	8 × 6
Husseinzadeh et al., 1988 [48]	47	labium minus	4,2 × 3
Chandeying et al., 1989 [49]	28	labium minus	4
Cliby et al., 1991 [50]	35	vulva	low than 1
Loret de Mola et al., 1993 [51]	49	Fourchette	2
Chen, 1994 [52]	68	vulva	3 × 2,5
Scurry et al., 1996 [53]	68	labium minus	4 × 3
Fawzi et al., 1997 [54]	78	vulva	5,5
Gil-Moreno et al., 1997 [55]	74	labium minus	9
Hierro et al., 2000 [56]	79	labium minus	2,5
Khoury-Collado et al., 2005 [57]	49	Bartholin gland	2
Pawar et al., 2005 [58]	35	labium majus	6 × 4
Mohit et al., 2009 [59]	50	labium majus	12 × 10
Sheikh et al., 2010 [60]	63	vulva	7 × 5
Lavazzo et al., 2011 [61]	63	labium majus	9

Table 1: Merkel cell carcinoma of the vulva [42].

MCC arise from external squamous mucosa, Bartolin gland duct, or minor vestibular glands [40]. MCC in this location vary in size from 1-12 cm in the greatest dimension (Figure 6) [42]. MCC of the vulva presents as a firm, mobile mass with edema, erythema, ulceration and pain [35]. The work of Nguyen et al., [35] brings the main information about the clinical presentation (Table 2) and histopathological evaluation (Table 3) of the vulvar MCC.

Clinical presentation of vulvar merkel cell carcinoma (35)	
	(n=17)
Characteristic	n (% or range)
Mean age (years) (28-79)	59.6
Mean tumor diameter (cm) (1.8-47.5)	7.5
Mean disease duration (months) (1-18)	4.7
Location (a)	
Labia majora	9 (52.9)
Labia minora	3 (17.6)
Paraclitoral	1 (5.9)
Bartholin gland	3 (17.6)
Intravaginal extension	4 (23.5)
Inguinal	1 (5.9)
Vulva, Unspecified	1 (5.9)
Clinical findings (a)	
Firm	2 (11.8)
Painless	3 (17.6)
Tender	5 (29.4)
Mobile	2 (11.8)
Pruritus	2 (11.8)
Swelling/edema	3 (17.6)
Ulceration	4 (23.5)
Erythema	2 (11.8)
A Sum exceeds 100% due to non-mutually exclusive categories	

Table 2: Clinical presentation of vulvar merkel cell carcinoma [35].

Lesions were predominantly located on the labia majora. Histopathological evaluation revealed small, undifferentiated cells with high N/C ratio, scanty cytoplasm. Immunostain results demonstrated higher positivity for pancytokeratine, than other markers. Management of the treatment is based on the surgical excision, vulvectomy or wide excision with 2 cm margins [35]. Recurrence and progression of the tumor are very common complcations after the treatment. There are no standardized protocols for treatment of vulvar MCC due to the rarity [62,63] The guidlines are same like in extravulvar MCC. In general MCC have an aggresive behavior, but those in the vulva are virulent with a 100% rate of inguinal node and

also distant metastases [62]. Prognosis of this carcinoma is very poor than prognosis of the MCC arising in other parts of the body [42].

Histopathological evaluation of vulvar merkel cell carcinomas [35]	
Characteristic	n (%)
Histologic finding (n=17)	
Small cells	**12(70.6)**
High N/C ratio, scant cytoplasm	**12 (70.6)**
Nests, islands, trabecular	11 (64.7)
Hyperchromatic	10 (58.8)
High mitotic index	8 (47.1)
Necrosis	6 (35.3)
Irregular nuclei	4 (23.5)
Fibrous	4 (23.5)
Apoptosis	4 (23.5)
Sheets	3 (17.6)
Hemorrhage	2 (11.8)
Ulceration	2 (11.8)
Electron microscopy (n=7)a	
Dense core granules	6 (85.7)
Intermediate filaments	5 (71.4)
Immunostaining (n=14)a	
Neuroendocrine markers	
Chromogranin	7 (50)
NSE	7 (50)
Synaptophysin	6 (42.9)
PGP 9.5	2 (14.3)
Keratin stains (n=13)a	
Pancytokeratin AE1/AE3	**7 (53.8)**
CAM5.2	4 (30.8)
Low molecular weight CK	3 (23.1)
CK7	1 (7.7)
CK8	2 (15.4)
CK18	3 (23.1)
CK19	1 (7.7)
CK20	4 (30.8)
Perinuclear dot/granular	**7(53.7)**

Table 3: Histopathological evaluation of vulvar merkel cell carcinomas [35].

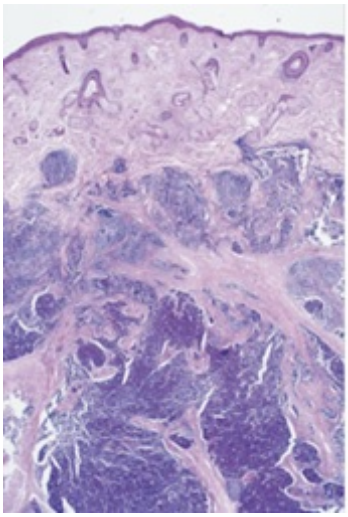

Figure 5: Scanning view shows extensive dermal infiltration by a small "blue" cell tumor [33].

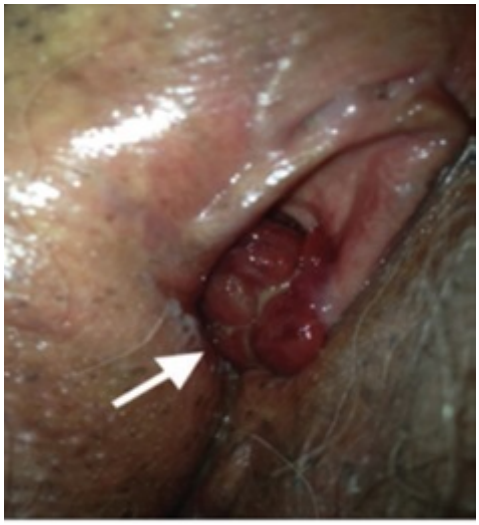

Figure 6: The primary vulvar MCC before biopsy (white arrow) [63].

Conclusion

The Merkel cells are still very interesting object of investigation because of its unique functions. They are not only the cells belong to one group with the same functions, but according Lucarz and Brand [15], functionally they can be classified into some subpopulations with different functions: mechanoreceptive, endocrine, chemosensitive. In clinical practice most studies are focus on their neuroendocrine functions and possible malignant transformation into the Merkel cell carcinomas [14]. Primary MCCs of the genitourinary system are very rare, aggressive and may be misinterpreted with other cancers of genitourinary system. There are no standardized protocols for treatment of vulvar MCC due to the rarity [62,63]. The guidlines are

same like in extravulvar MCC. In general MCC have an aggresive behavior, but those in the vulva are virulent with a 100% rate of inguinal node and also distant metastases [62]. Prognosis of this carcinoma is very poor than prognosis of the MCC arising in other parts of the body [42]. For pathologists it is very important to differentiate it from other more common tumors of the genitourinary system.

References

1. Tachibana T, Nawa T (2002) Recent progress in studies on Merkel cell biology. Anat Sci Int 77: 26-33.
2. Boulais N, Misery L (2007) Merkel cells. J Am Acad Dermatol 57: 147-165.
3. Merkel F (1875) Tastzellen und Tastkor perchen bei den Hausthieren und beim menschen. Arch. Mikrosk. Anat 11: 636-652.
4. Boot PM, Rowden G, Walsh N (1992) The distribution of Merkel cells in human fetal and adult skin. Am J Dermatopathol 14: 391-396.
5. Moll I, Roessler M, Brandner JM, Eispert A, Houdek P, et al. (2005) Human Merkel Cells-aspects of cell biology- distribution and functions. Eur J Cell Biol 84: 259-271.
6. Lacour JP, Dubois D, Pisani A, Ortonne JP (1991) Anatomical mapping of Merkel cells in normal human adult epidermis. Br J Dermatol 125: 535-542.
7. Hartschuh W, Grube D (1979) The Merkel cell: A member of the APUD cell system. Fluorescence and electron microscopic contribution to the neurotransmitter function of the Merkel cell granules. Arch Dermatol Res 265: 115-122.
8. Harmse JL, Carey F, Baird SR (1999) Merkel cells in the human oesophagus. J Pathol 189: 176-179.
9. May CA, Osterland I (2013) Merkel cell distribution in the human eyelid. Eur J Histochem 57: 225-227.
10. Cold CJ, Taylor JR (1999) The prepuce. Br J Urol 8: 34-44.
11. Schober JM, Martin-Alguacil N, Cooper RS (2016) Identification of Merkel cells in the labia minora skin of prepubertal girls. J genit Syst Disor 5: 2.
12. Munde PB (2013) Pathophysiology of Merkel cells. J Oral Maxillofac Pathol 17: 408-412.
13. Garant PR, Feldman J, Cho MI, Cullen MR (1980) Ultrastructure of Merkel cells in the hard palate of the squirrel monkey (Saimiri sciureus). Am J Anat 157: 155-167.
14. Halata Z, Grim M, Bauman KI (2003) Friedrich Sigmund Merkel and his "Merkel cell", morphology, development, and physiology: review and new results. Anat Rec A Discov Mol Cell Evol Biol 271: 225-239.
15. Lucarz A, Brand G (2007) Current considerations about Merkel cells. Eur J Cell Biol. 11: 12-21
16. Crowe R, Whitear M (1978) Quinacrine fluorescence of Merkel cells in Xenopus leavis. Cell Tissue Res 190: 273-283.
17. Moll R, Moll I, Franke WW (1984) Identification of Merkel cells in human skin by specific cytokeratin antibodies: changes of cell density and distribution in fetal and adult plantar epidermis. Differentiation 28: 136-154.
18. Fukuda J, Ishimine H, Masaki Y (2003) Long-term staining of live Merkel cells with FM dyes. Cell Tissue Res 311: 325-332.
19. Manju A, Ming Z (2011) Merkel cell carcinoma of the genitourinary tract. Arch Pathol Lab Med 135: 1067-1071.
20. Richards J, Prada DM (1997) Uranaffin reaction: a new cytochemical technique for the localization of adenine nucleotides in organelles storing biogenic amines. J Hystochem Cytochem 25: 1322-1336.
21. Haeberle H, Fujiwara M, Chuang J (2004) Molecular profiling reveals synaptic release machinery in Merkel cells. Proc Natl Acad Sci 101: 503-508.
22. Tachibana T (1995) The Merkel cell: recent findings and unresolved problems. Arch Histol Cytol 58: 379-396.
23. Kim DK, Holbrook KA (1995) The appearance, density, and distribution of Merkel cells in human embryonic and fetal skin: their relation to sweat gland and hair follicle development. J Invest Dermatol 104: 411-416.
24. Toker C (1972) Trabecular carcinoma of the skin. Arch Dermatol 105: 107-110.
25. Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, et al.(2008) Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol Mar 58: 375-381.
26. Smith VA, Camp ER, Lentsch EJ (2012) Merkel cell carcinoma: identification of prognostic factors unique to tumors located in the head and neck based on analysis of SEER data. Laryngoscope 122: 1283-1290.
27. Schadendorf D, Lebbé C, Hausen A, Avril MF, Hariharan S, et al. (2017) Merkel cell carcinoma: epidemiology, prognosis, therapy and unmet medical needs. European Journal of cancer 71: 53-69.
28. Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, et al. (2010) Merkel cell carcinoma demographics,morphology, and survival based on 3870 cases: apopulation-based study. J Cutan Pathol 37: 20-27.
29. Agbai ON, Buster K, Sanchez M, Hernandez C, Kundu RV, et al. (2014) Skin cancer and photoprotection in people ofcolor: a review and recommendations for physicians and the public. J Am Acad Dermatol 70: 748-762.
30. Kempf W, Mertz KD, Hofbauer GF, Tinguely M (2013) Skin cancer in organ transplant recipients. Pathobiology 80: 302-309.
31. Wong SQ, Waldeck K, Vergara IA, Schröder J, Madore J, et al. (2015) UV-associated mutations underlie the etiology of MCV-negative Merkel cell carcinomas. Cancer Res 75: 5228-5234.
32. Nghiem P, McKee PH, Haynes HA (2001) Merkel cell (cutaneous neuroendocrine) carcinoma. Cancer J Clin 48: 6-29.
33. Johansson L, Tennvall J, Akerman M (1990) Immunohistochemical examination of 25 cases of Merkel cell carcinoma: a comparison with small cell carcinoma of the lung and oesophagus, and a review of the literature. Apmis 98: 741-752.
34. Nguyen (2017) Clinical features and treatment of vulvar Merkel cell carcinoma: a systematic review Gynecologic Oncology Research and Practice 4: 2.
35. Becker JC (2010) Merkel cell carcinoma. Ann Oncol 21: 81-85.
36. Hodgson NC (2005) Merkel cell carcinoma: changing incidence trends. Journal of surgical oncology 89: 1-4.
37. Agelli M, Clegg LX (2003) Epidemiology of primary Merkel cell carcinoma in the United States. J Am Acad Dermatol 49: 832-841.
38. Bichakjian, Lowe, Lao, Sandler, Bradford, et al. (2007) Merkel cell carcinoma: critical review with guidelines for multidisciplinary management. Cancer 110: 1-12.
39. Kokoska ER, Kokoska MS, Collins BT, Stapleton DR, Wade TP (1997) Early aggressive treatment for Merkel cell carcinoma improves outcome. Am J Surg 174: 688-693.
40. Linjawi A, Jamison WB, Meterissian S (2001) Merkel cell carcinoma: important aspects of diagnosis and management. Am J Surg 67: 943-947.
41. Manju A, Ming Z (2011) Merkel cell carcinoma of the genitourinary tract, Arch Pathol Lab Med 135: 1067-1071.
42. Best TJ, Metcalfe JB, Moore RB, Nguzen GK (1994) Merkel cell carcinoma of the scrotum. Ann Plast Surg 33: 83-85.
43. Tomic S, Warner TF, Messing E, Wilding G (1995) Penile Merkel cell carcinoma. Urology 45: 1062-1065.
44. Tang CK, Toker C, Nedwich A, Zaman AN (1982) Unusual cutaneous carcinoma with features of small cell (oat cell-like) and squamous cell carcinomas. A variant of malignant Merkel cell neoplasm. Am J Dermatopathol 4: 537-548.
45. Bottles K, Lacey CG, Goldberg J, Lanner-Cusin K, Hom J, et al. (1984) Merkel cell carcinoma of the vulva. Obstet Gynecol. 63: 61S-65S.
46. Copeland LJ, Cleary K, Sneige N, Edwards CL (1985) Neuroendocrine (Merkel cell) carcinoma of the vulva: a case report and review of literature. Gynecol Oncol. 22: 367-378.

47. Husseinzadeh N, Wesseler T, Newman N, Shbaro I, Ho P (1988) Neuroendocrine (Merkel cell) carcinoma of the vulva. Gynecol Oncol. 29: 105-115.
48. Chandeying V, Sutthijumroon S, Tungphaisal S (1989) Merkel cell carcinoma of the vulva: a case report. Asia Oceania J Obstet Gynaecol 15: 261-265.
49. Cliby W, Soisson AP, Berchuck A, Clarke-Pearson DL (1991) Stage I small cell carcinoma of the vulva treated with vulvectomy, lymphadenectomy, and adjuvant chemotherapy . Cancer 67: 2415-2417.
50. Mola JR, Hudock PA, Steinetz C, Jacobs G, Macfee, M et al. (1993) Merkel cell carcinoma of the vulva. Gynecol Oncol 51: 272-276.
51. Chen KT (1994) Merkel's cell (neuroendocrine carcinoma) of the vulva. Cancer 73: 2186-2191.
52. Scurry J, Brand A, Planner R, Dowling J, Rode J (1996) Vulvar Merkel cell tumor with glandular and squamous differentiation. Gynecol Oncol 62: 292-297.
53. Fawzi HW, Cross PA, Buckley CH, Monaghan JM (1997) Neuroendocrine (Merkel cell) carcinoma of the vulva. J Obstet Gynaecol 17: 100-101.
54. Gil-Moreno A, Garcia-Jiménez A, González-Bosquet J et al. (1997) Merkel cell carcinoma of the vulva. Gynecol Oncol 64: 526-532.
55. Hierro I, Blanes A, Matilla A, Muñoz S, Vicioso L, et al. (2000) Merkel cell (neuroendocrine carcinoma) of the vulva: a case report with immunohistochemical and ultrastructural findings and review of literature. Pathol Res Pract 196: 503-509.
56. Khoury-Collado F, Elliott KS, Lee YC, Chen PC, Abulafia O (2005) Merkel cell carcinoma of the Bartholin's gland. Gynecol Oncol 97: 928-931.
57. Pawar R, Vijayalakshmy AR, Khan S, Lawati FA (2005) Primary neuroendocrine carcinoma (Merkel's cell carcinoma) of the vulva mimicking a Bartholin's gland abscess. Ann Saudi Med 25: 161-164.
58. Becker JC (2010) Merkel cell carcinoma. Ann Oncol 21: 81-85.
59. Mohit M, Mosallai A, Monabbati A, Mortazavi H (2009) Merkel cell carcinoma of the vulva. Saudi Med J 30: 717-718.
60. Sheikh ZA, Nair I, Vijaykumar DK, Jojo A, Nandeesh M (2010) Neuroendocrine tumor of vulva: A case report and review of literature. J Cancer res ther 6: 365-366.
61. Lavazzo C, Terzi M, Dadioti P, Dertimas V, Vorgias G (2011) Vulvar Merkel carcinoma: a case report. Case Rep med 54: 69-72.
62. Chen CH, Wu YY, Kuo KT, Liau JY, Liang CW (2015) Combinedsquamous cell carcinoma and Merkel cell carcinoma of the vulva:Role of human papillomavirus and Merkel cell polyomavirus. JAAD Case Rep 1: 196-199.
63. Butorac D, Djaković I, Kruljac I, Kuna K (2016) Vulvar Merkel cell carcinoma-case report. Ginekol Pol 84: 385-389.