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Case report

Fine Needle Aspiration Cytology of Metastatic Merkel Cell Carcinoma

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A B S T R A C T

Merkel cell carcinoma (MCC) is uncommon cutaneous malignant neuroendocrine tumour of the elderly people with rapidly growing skin nodules found frequently on sun-exposed areas of the body. MCC is often an aggressive tumour with high tendency for local recurrence, lymph node involvement and distant metastases. This paper reports a case of metastatic MCC diagnosed by fine needle aspiration cytology (FNAC), flow cytometric deoxiribonucleated acid (DNA) analysis, pathohistology and electron microscopy. The cytological features in aspirate (stained with Papenheim and Papanicolaou staining) included increased cellularity, discohesive groups of small-to-medium size malignant cells with uniform, round-to-oval nuclei with moulding effect, fine chromatin, multiple micronucleoli and scanty cytoplasm. DNA flow cytometric analysis of the aspirate showed unexpected results for clinically aggressive behaviour of this tumour (the patient died after 21 months), and revealed that tumour contained diploid peak with DNA index of 1.1. The proliferation was high with elevated S-phase fraction (21%). The cytological diagnosis of possible metastatic MCC was confirmed by histological one as well as by electron microscopy presented the pathognomonic features for this tumour: dense-core neurosecretory granules with diameter of 100–250 nm surrounded by whorls of intermediate filaments. MCC provides an enormous challenge for the morphologist because of a wide range of differential diagnosis and for the clinician because this tumour has a highly malignant potential for local recurrence, nodal and distant spread and very often is combined with other tumours. Therefore it is important to perform FNAC of different lesions in the same patient because it can distinguish MCC from the other tumours.

***Key words**: fine needle aspiration cytology, Merkel cell carcinoma, flow cytometry, electron microscopy*

Introduction

Merkel cell carcinoma (MCC) was first described by Toker in 1972 as trabecular carcinoma of the skin[1]. In 1978 with electron microscopy Tang and Toker identified membrane-bound, neurosecretory, dense-cored granules in the malignant cells and pointed to their possible origin from Merkel cells (MCs)[2]. Because MCs are the only skin cells containing such granules, as described by Merkel in 1875, the tumour was named after him[3].

MCC also known as neuroendocrine carcinoma of the skin, trabecular carcinoma of the sweat glands, small cell neuroepithelial tumour of the skin, cutaneous apudoma, merkelioma, primary small cell (oat cell-like) carcinoma of the skin with endocrine differentiation, is a rare and very aggressive malignant tumour commonly found on the white, sun-exposed skin of elderly patients[4–6]. The average age of diagnosis is 69 years (range 7 to 104). Both sexes are affected, but there seems to be a male predominance of 3:1[7]. The head and the neck as well as limbs are the most common primary sites[4,8]. These tumours usually arise in the dermis and subcutaneous tissues. Immunocytochemistry reveals a double differentiation, both neuroendocrine and epithelial because tumour cells show

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positive labelling against neurofilament protein and cytokeratin (CK) and contain neuron-specific enolase (NSE)[9–11].

This neoplasm is usually characterised by local recurrence, regional lymph node and distant metastases. Prognosis depends on gender, dissemination of illness, age of patient, tumour size and location and histological characteristics[6,7].

In the treatment, wide surgical excision like in malignant melanoma with the nearby lymph node dissection (if the sentinel lymph node is positive) is recommended[12]. Radio or chemo-therapy treatment of extensive local or distant metastatic disease results in only short-term palliative response and usually 50% of patients die within 20 months[13,14].

This paper reports a case of metastatic MCC diagnosed by fine needle aspiration cytology (FNAC), pathohistology and electron microscopy. According to our knowledge from the available literature, it appears to be the third report of flow cytometric deoxiribonucleated acid (DNA) analysis of MCC and the first one performed from the aspirate[15,16].

Case Report

A 75-year-old woman was admitted to the other hospital because of 3 cm nodule with central ulceration behind the left ear that was occasionally bleeding. Medical history data revealed that the problems had started 11 months ago as a red, painless nodule of 0.5 cm in diameter, that was considered to be irritation caused by the hearing aid device (worn for the past ten years). The tumour was extirpated and pathohistologically diagnosed as MCC. The patient did not receive any chemotherapy or radiotherapy. Three months later, without medical history of previous trauma, a strong pain in the right leg was observed and X-ray examination showed a pathological multifragmentary fracture of the right tibia and fibula. Six months later (20 months from the first symptoms) the patient was admitted to our hospital due to advanced hypercalcaemia. She was bed-ridden because of pathological multifragmentary fracture of the right lower leg and had numerous individual, irregular, soft, movable nodules on both sides of the neck 1–4 cm in diameter, up and down the clavicle, in the pectoral region, in the right inguinal region and on the left upper arm.

FNAC of the nodule on the right side of the neck, supraclavicular lymph node and nodule on the left arm was performed using a 23-gauge needle and a 20-mL syringe. One part of aspirate was used for preparation of cytological smears that were stained by Papenheim and Papanicolaou staining and the rest was used for DNA analysis by flow cytometry.

The smears were highly cellular consisting of three-dimensional aggregates or loosely cohesive cell clusters, isolated cells and naked nuclei (Figure 1). The cells were small to medium-sized, monomorphic round to oval with large oval to irregular nuclei with fine or coarse granular chromatin, sometimes with moulding effect and scanty indistinct cytoplasm (Figure 2). In the Papanicolaou-stained smears the nuclei appeared round and vesicular, with multiple inconspicuous nucleoli while cytoplasm could not be readily identified and appeared as a thin, clear perinuclear rim (Figure 3). The background was granular and consisted of lysed red blood cells admixed with necrotic cells and few lymphocytes. Few mitosis and »intermediate filament buttons« were found. The cytological diagnosis of probable metastatic Merkel cell carcinoma was established.

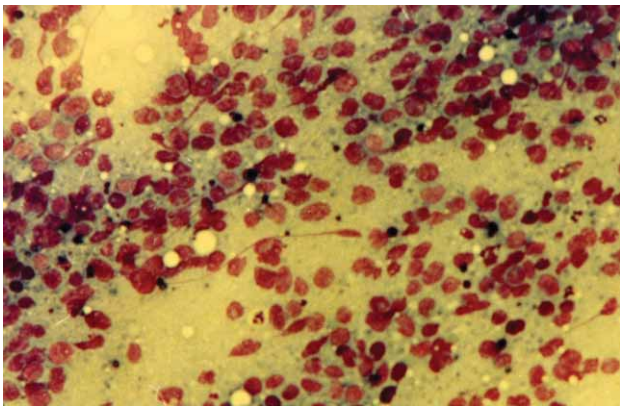

Fig. 1. A highly cellular FNA smear consists of loosely cohesive cell clusters, isolated cells and naked nuclei (Papenheim stain, x400).

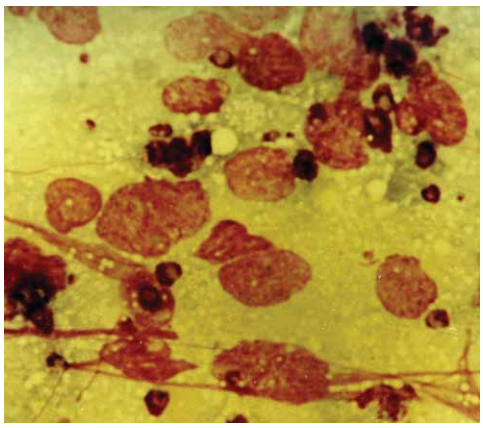

Fig. 2. High-power magnification shows tumour cells with large irregular nuclei with moulding effect, finely granular chromatin, inconspicuous nucleoli and indistinct cytoplasm and few lymphocytes (Papenheim stain, x1000).

We made a quantitative flow cytometric DNA analysis obtained from the fresh aspirates which requires the preparation of a single cell suspension, removal of the cell membrane and cytoplasm, treatment with ribonuclease (RNase) and staining with DNA-specific dye (we used propidium iodide). Although the MCC in our patient showed aggressive behaviour, the flow cytometric DNA analysis of the tumour gave the unexpected results: the tumour was diploid according to DNA histograms and DNA index (1.1) but the percentage of cells in the

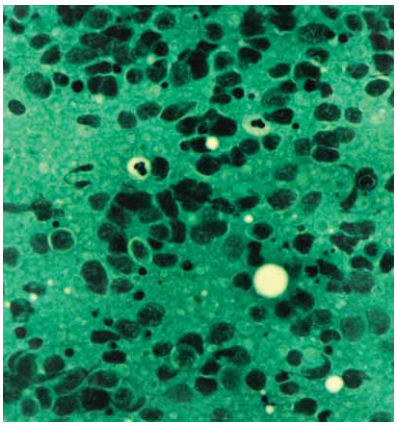

Fig. 3. Aspirate consists of loosely cohesive monotonous round to oval tumour cells with vesicular and round nuclei with moulding effect. The cytoplasm consists of a thin, unstained perinuclear rim and there are few »intermediate filament buttons«. The background is granular consisting of lysed red blood cells and cellular debris (Papanicolaou stain, x400).

S-phase was high: 21% (normal value up to 10%) showing an unregulated proliferation.

The nodule from the arm was chosen to be resected and the cytological diagnosis was confirmed by a histological one. The specimen consisted of skin tissue with a dome-shaped formation 3.0×2.5×1.5 cm defective in the central part, 2 cm in diameter and 0.5 cm deep. The tissue was fixed in 10% formalin, routinely processed. Immunohistochemistry was carried out on paraffin sections using standard techniques with antibodies against epithelial membrane antigen (EMA), NSE, common leukocyte antigen (LCA), S-100 and vimentin.

The tumour tissue was characterised by atypical cells with round to oval nuclei, granulated chromatin, indistinct cytoplasm and high nuclear/cytoplasmic ratios. The tumour cells infiltrated around a blood vessel and many of them were pyknotic (Figure 4). Tumour cells formed

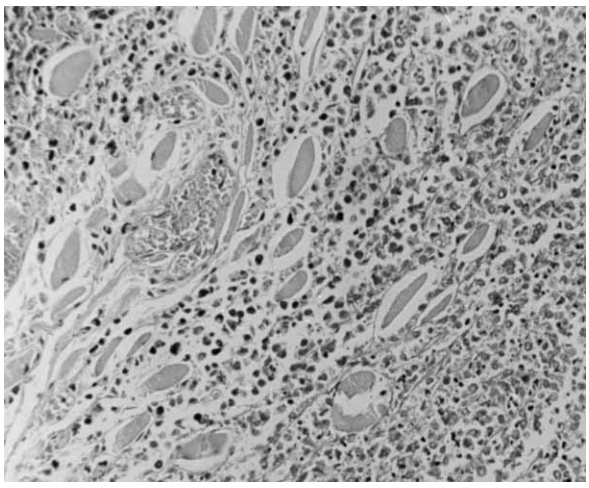

Fig. 4. Tissue section shows tumour cells with high nuclear/cytoplasmic ratios infiltrate around a blood vessel. Many cells are pyknotic (hematoxylin and eosin stain, x400).

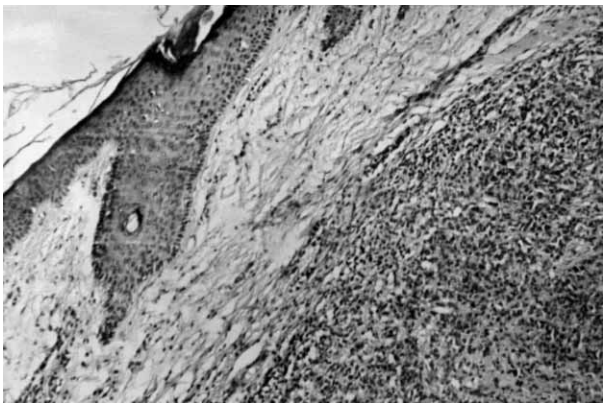

Fig. 5. Tumour cells form nests and trabecules in the dermis while the epidermis is intact (hematoxylin and eosin stain, x400).

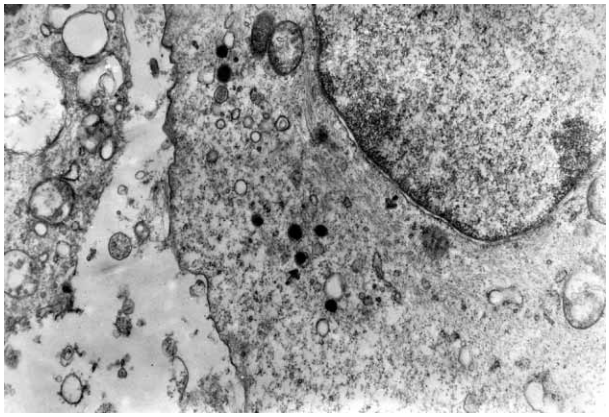

Fig. 6. The cytoplasm contains dense-core neurosecretory granules surrounded by halo (arrow). The paranuclear bundles of intermediate filaments are situated near the nucleus (arrow) (electron microscopy, x18200).

nests and trabecules in the dermis while the epidermis was intact (Figure 5). There were numerous mitoses. Tumour tissue was not found on the edges and at the base. On immunostaining, NSE and EMA were positive, while LCA, S-100 and vimentin were negative. Pathohistological diagnosis of metastatatic Merkel cell carcinoma was established.

Electron microscopy confirmed pathohistological diagnosis. Examination with the electron microscopy showed poorly cohesive tumour cells attached by zonula-adherens-type junctions. The cells were polygonal with round, large nuclei containing finely dispersed chromatin with small nucleoli and a narrow rim of peripheral heterochromatin. The cytoplasm contained clusters of dense-core neurosecretory granules of 100–250 nm in diameter surrounded by halo and peripherally situated just beneath the cell membranes (Figure 6). The paranuclear bundles or whorls of intermediate filaments were situated near the nucleus. Unfortunately the patient died five days later, 21 months since the primary MCC has been detected. Permission for autopsy was denied.

Discussion and Conclusion

Although MCC is a rare neuroendocrine tumour which is presumed to originate from MCs of the skin, it was noticed that mature MCs do not cause MCC[17]. Besides, the tumour arises in the dermis while the epidermis containing Merkel cells remains intact. That fact led to new ideas about the origin and the name of the tumour. In 1990 Kivela and Tarkkanen indicated that Merkel cell carcinoma might have developed from precursor cells which gave rise to keratinocytes and MCs[18].

The pathogenesis is also doubtful. Because MCC mostly occurs on the head, neck and extremities, sunlight has been indicated as a probable cause. Miller and Rabkin have reported that the UVB index is correlated with the incidence of MCC[19]. Immunosuppression has also been associated with MCC and therefore it occurs more frequently in patients with renal transplantation, with HIV infection and with chronic lymphatic leukaemia and lymphoma disease[20–22]. A recently discovered virus called Merkel cell polyomavirus (MCV) is suspected to develop the majority of MCC, because 80% of MCC tumours have this virus integrated in a monoclonal pattern indicating that the infection was present in a precursor cell before it became cancerous[23]. Beside MCC in 11% of patients other neoplasms can be found, such as chronic lymphocytic leukaemia, plasmacytoma, non-Hodgkin lymphoma (NHL), carcinoma of breast, lung, small intestine, pancreas, salivary glands, prostate and brain[6,8]. One of two patients with Merkel cell carcinoma on the head or neck has another skin tumour: the most common are squamous cell carcinoma, basal cell carcinoma, melanoma and sometimes Bowen's disease[6,24]. Therefore it is very important to perform FNAC of patient's different nodules to be sure that all of them are MCC, as we did.

The most common primary site of the MCC are the head and neck (>50% of cases), especially the eyelids, the extremities (40% of cases) and the trunk, most frequently the gluteal region (10% of cases)[1,6,7,13,25]. In our patient the primary tumour was situated behind the right ear. Local recurrence is common (27–60%), metastases to nearby regional lymph nodes occur in 45 to 91% of patients and disease dissemination is observed in 18 to 52% of patients usually within the 2 years of primary diagnosis as we had in our patient[7]. Secondary sites of involvement include the skin, liver, bone, lymph nodes, brain, spine, lungs, testis, pancreas, colon, uterus, parotid gland[4,5,7,26–29]. Our patient had metastases in regional and distant lymph nodes and skin and probably in bones. Several cases of metastases to lymph nodes have been described and the primary lesion has not been found[5].

MCC looks like firm, red or skin coloured, painless nodule with vaguely defined borders. It can vary in size from the usual 1–2 cm to even 16 cm. Ulceration and bleeding usually occur in larger tumours, as observed in our patient. The diagnosis could not be made clinically and the disease can be mistaken for other cutanous tumours[8]. Therefore FNA of the nodules had to be performed because the Merkel cell carcinoma could be diagnosed by cytological examination with the use of ancillary techniques[4,9–11,16,26,30–36] although some authors suggest that histology is only conclusive[6]. Domagala and colleagues first described a peculiar cytological feature of neoplastic MCs possessing »intermediate filament buttons« which were described as »pale-pink, homogeneous, relatively dense, well-circumscribed round-or-oval buttons of cytoplasm found in a perinuclear location« which could be observed either by staining with intermediate filament-specific antibodies using immunofluorescence or by their appearance in hematoxylin-and-eosin-stained smears[31]. Some other authors confirmed that the presence of intermediate filament buttons coexpressing keratins and neurofilaments in FNA smears is virtually diagnostic of MCC[9,32,34]. Gherardi and colleagues demonstrated that the accumulation of intermediate filaments in the cytoplasm of neoplastic MCs is also readily seen in air-dried Romanowsky-stained cytological samples as clear blue-stained perinuclear rim and peculiar paranuclear globules of varying size[30]. Although cytological appearance of MCC is usual described like highly cellular smears of loosely clustered and individual, monomorphic tumour cells with round to oval, regularly contoured nuclei with scanty cytoplasm, Hallman et al. presented two atypical cases of MCC with a spectrum of polymorphism ranging from moderately complex nuclear membranes with cleaves and protrusions in one case to large, markedly bizarre, convoluted nuclei and multinucleate tumour cells in another case[33]. We detected a moderate degree of pleomorphism in the FNA smears in our patient: irregular nuclei and cell moulding.

Numerous studies have reported an association between abnormalities in DNA content and clinical course in variety of human carcinomas. Although DNA flow cytometry has been advocated as an independent prognostic indicator for the assessment of tumour behaviour, its clinicopathological significance remains controversial. The prognostic importance of an abnormal DNA histogram for an individual patient must be assessed on the basis of the relevant data base for that particular tumour type. The highly aggressive neuroendocrine carcinomas (like MCC) usually are composed of tumour cells with nuclei displaying diploid, normal DNA pattern in the primary and metastatic carcinoma, while clear-cut aneuploid DNA histograms can be found in the neoplastic cell nuclei of clinically and histopahtologicallly completely benign neuroendocrine adenomas[37]. Visscher et al. performing DNA flow cytometric analysis from paraffin blocks of the 13 primary and metastatic MCC got 12 diploid and one aneuploid DNA content and all 13 elevated S-phase fractions (mean 15%, range 8 to 22%) similar to our result[15]. Yang et al. presented DNA analysis of the primary MCC in submadibular gland that was aneuploid with elevated proliferation[16].

There are three distinct types of MCC described in pathohistology according to cytomorphologic characteristics of the individual cells as well as their architectural arrangement: the intermediate cell type which is the most frequent, the small cell type, analogous to oat cell

carcinoma of the lung and the large cell type[38]. The cells can be arranged in compact clusters, pseudorosettes or trabecules, or they are diffusely dispersed[39]. Some tumours are infiltrated by lymphocytes and plasma cells or surrounded by fibrosis and granular tissue especially when ulcerated. Cells are located in the dermis and spread vertically invading the subcutaneous tissue, fat tissue and muscles, reaching the epidermis but not spreading to it and leaving it intact.

Other tumours may look cytological and histological similar to MCC: NHL, metastatic small cell lung carcinoma, poorly differentiated squamous skin cancer, amelanotic melanoma, basal cell carcinoma, anaplastic sweat glands cancer, cutaneous neuroblastoma, carcinoid, metstatic medullar thyroid cancer, extraskeletal Ewing's sarcoma, embryonal rhabdomyosarcoma, Wilm's tumour[4,9,11,16,27,33,36]. Immunocytochemistry (especially on cell block preparations) and immunohistochemistry helps us differentiate one from the other[4,9–11,16,30,32–34]. For MCC cells NSE staining is positive (diffuse cell dispersion or paranuclear globules and a thin perinuclear rim) which is a good marker for neuroendocrine cells and it was positive in our patient. Neurofilaments and chromogranin A create paranuclear globules as well as CK 20 and EMA thus confirming the epithelial character of the tumour, while thyroid transcription factor (TTF-1) is negative whereas the small-cell lung carcinoma reveals TTF-1 positive and CK 20 negative[10,11]. Sometimes bioactive peptides released from secretory granules such as calcitonin, somatostatin and gastrin can be found, which is characteristic for apudomas. On the other hand, common leukocyte antigen (LCA), vimentin and S-100 protein are negative like in our patient.

Although MCC can be recognised by its characteristic light microscopic features, electron microscopy is advisable and sometimes is the key of diagnosis as in our patient[17]. The characteristics of the tumour are as follows: 1. peripherally membrane-bound electron dense-core neurosecretory granules 100–250 nm in diameter surrounded by a halo, which is patognomonic for this tumour; 2. spinous cytoplasm extensions; 3. patognomonic paranuclear intermediate filaments (as opposed to small cell lung cancer where cytokeratin and neurofilaments are broadly perinuclearly located); 4. weak cell cohesion and zonula adherens (less commonly desmosomal) junction[16–17,25–26,33].

We can conclude that Merkel cell carcinoma provides an enormous challenge for the morphologist because of a wide range of differential diagnosis as well as for the clinician due to this tumour's high malignant potential for local recurrence, nodal and distant spread and very often found in combination with other tumours. Therefore, FNAC of different lesions in the patients with multiple neoplasms is important in differentiating MCC from other tumours. Of course, the best outcome is achieved by multidisciplinary management of MCC with input from the cytologist, surgeon, radiologist, oncologist and pathologist.

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ASPIRACIJSKA CITOLOGIJA METASTATSKOG KARCINOMA MERKELOVIH STANICA

S A Ž E T A K

Karcinom Merkelovih stanica je rijedak maligni neuroendokrini tumor kože starijih ljudi koji se manifestira brojnim brzo-rastućim čvorovima kože prvenstveno na područjima tijela izloženih suncu. To je često vrlo agresivan tumor s tendencijom brze pojave lokalnih recidiva uz zahvaćanje regionalnih limfnih čvorova kao i pojave udaljenih metastaza. U ovom radu smo prikazali pacijenticu s karcinomom Merkelovih stanica dijagnosticiranim citološki, DNK analizom punktata protočnim citometrom, patohistološki i analizom elekronskim mikroskopom. Razmazi citoloških punktata obojenih po Papenheim-u i Papanicolaou-u su jako celularni s rahlim grupama malih do srednje velikih malignih stanica ovalne do nepravilne jezgre ponegdje s utiskivanjem stanica i jezgara, fino zrnatog kromatina, brojnih jezgrica i oskudne citoplazme. Usprkos agresivnom ponašanju tumora (pacijentica je umrla nakon 21 mjeseca), DNK analiza protočnim citometrom je pokazala da je tumor diploidan s DNK indeksom 1.1. Međutim, tumor ima povećanu i nereguliranu proliferaciju (u S-fazi je bilo prisutno 21% stanica). Citološka dijagnoza mogućeg metastatskog karcinoma Merkelovih stanica je potvrđena histološki i elektronsko-mikroskopskom analizom kojom su se uočile patognomonične promjene za ovaj tumor: u citoplazmi tumorskih stanica uzduž unutarnje strane stanične membrane nađene su nakupine okruglastih, jednolikih neurosekretornih granula s elektronski gustim jezgrama, a uz jezgru su nađene paranuklearne nakupine intermedijarnih filamenata. Karcinom Merkelovih stanica predstavlja veliki izazov za morfologe zbog široke palete diferencijalne dijagnoze različitih tumora, a također i za kliničare jer ovaj tumor ima veliki maligni potencijal te brzo dolazi do lokalnog recidiva, metastaza u regionalne limfne čvorove kao i pojave udaljenih metastaza. Osim toga karcinom Merkelovih stanica je vrlo često udružen i s drugim malignim tumorima. Zbog toga je vrlo važno punktirati više lezija u pacijenata koji imaju multiple tvorbe, kako bi se citološki razlučio karcinom Merkelovih stanica od mogućih drugih tumora.