

Histopathological aspects of unusual skin tumors with clinical correlations

Ph.D.Thesis

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Abbreviations

BCC: basal cell carcinoma

ChrA: chromogranin A

CK20: cytokeratin 20

DN: dysplastic nevus

EMA: epithelial membrane antigen

IFN: interferon

IH: immunohistochemistry

LT1 and LT3: viral large T protein

NMM: nodular malignant melanoma

NSE: neuron specific enolase

MCC: Merkel cell carcinoma

MCV: Merkel cell polyomavirus

MM: malignant melanoma

SCC: squamous cell carcinoma

SSM: superficial spreading melanoma

VP1: viral capsid protein

1. Publications related to the subject of the thesis

Journal articles

- I. Korom Irma, Oláh Judit, Gyulai Rolland, **Varga Erika** Szokatlan megjelenésű melanomákról. *Bőrgyógy. Vener. Szle.* 75: 133-136, 1999.
- II. Oláh Judit, Gyulai Rolland, Varga János, Mohos Gábor, Kapitány Klára, Papos Miklós, Pávics László, **Varga Erika**, Korom Irma, Dobozy Attila: Őrszemnyirokcsomó-biopsziával szerzett tapasztalataink melanoma malignumban. *LAM* 11: 536-41, 2001.
- III. Oláh Judit, Gyulai Rolland, Korom Irma, **Varga Erika**, Dobozy Attila: Tumour regression predicts higher risk of sentinel node involvement in thin cutaneous melanoma. *Br J Dermatol* 149: 662-663, 2003.
- IV. Korom Irma, Oláh Judit, **Varga Erika**, Kapitány Klára: Melanoma malignum gyermekkorban. *Bőrgyógy Vener Szle* 80: 275-278, 2004
- V. Korom Irma, Oláh Judit, **Varga Erika**, Földes Márta, Kemény Lajos: Ritka melanocytás naevusok: clonalis naevusok. Rare melanocytic nevi: clonal nevi. *Bőrgyógy Vener Szle* 82: 96-99, 2006
- VI. **Varga Erika**, Kiss Mária, Szabó Kornélia, Kemény Lajos: Detection of Merkel cell polyoma virus DNA in Merkel cell carcinomas. *Br J Dermatol* 161 :930-2, 2009
- VII. **Varga Erika**, Korom Irma, Varga János, Kohán József, Kemény Lajos, Oláh Judit: Malignant melanoma and dysplastic nevi in decorative tattoos: case reports. *J Cutan Pathol* – in press
- VIII. **Varga Erika**, Korom Irma, Raskó Zoltán, Kis Erika, Varga János, Oláh Judit, Kemény Lajos: Neglected basal cell carcinomas of the 21st century. *Journal of Skin Cancer* – in press

2. Introduction

As a pathologist, dermatologist and dermatopathologist – if it could be listed as separate entities at all in my professional life – I always considered the diagnosis of an unusual skin tumor as a special challenge. My first presentation as a dermatology resident at a conference was about the incidence and characteristics of rare melanocytic tumors. During the following years this subject became one of my focus interests as we are lucky to have the possibility of diagnose almost 5.000 cases per a year. The original group of rare melanocytic tumors has been expanded by now to all rare cutaneous neoplasm. Their clinical appearance, histopathological characteristics and treatment modalities became the aims of my work and thesis.

2.1 Rare melanocytic tumors

Apart from the conventional, classic forms of melanocytic tumors (junctional, intradermal, compound) the recognition of different rare variants are very important. The knowledge of their clinical and histopathological features is essential in the differential diagnosis of the various benign forms and for the differentiation from malignant melanoma.

2.1.1. Clonal nevi

Ball and Golitz ¹ in 1994 presented a new and unusual variant of melanocytic nevus called clonal nevus. They analyzed the dermatopathological cases retrospectively between 1987-1993 and found 73 such nevi. Clonal nevi represent melanocytic nevi with dermal foci of heavily pigmented, epithelioid melanocytes within a banal melanocytic nevus. The typical clinical history in clonal nevus is a recently presenting dark area in a preexisting nevus. This anamnesis can occur in dysplastic and deep penetrating nevi and even in malignant melanoma so the clinical diagnosis is often difficult.

The histopathological picture is usually typical: well circumscribed, large nests of epithelioid melanocytes could be found in the upper dermal part of a banal compound or dermal melanocytic nevus. The cells contain dust-like melanin pigment without significant atypia. Mitotic figures are absent or very rare. The nests are surrounded by melanophages.

This type of clonal focus is presented in the 5-80% (average 20%) of the nevus and can be detected even at low-power magnification. Clonal nevi can be clinically and sometimes histopathologically resemble to deep penetrating nevus, combined nevus, cellular blue nevus or plexiform spindle cell nevus. Previously they were considered as a variant of combined nevi (combined nevus and Spitz' nevus, combined nevus and deep penetrating nevus, combined nevus with pagetoid cells) or they were presented as inverted A-type nevus.² Sometimes it was misdiagnosed clinically or histopathologically as malignant melanoma.

Ball and Golitz¹ presented mainly the histopathological features and the differential diagnostic difficulties. Huynh and co-workers³ in 2004 summarized the characteristic clinical appearance. Their five cases and the fotodocumentations help establishing the proper clinical diagnosis. According to their observation the recently appearing central or eccentric flat dark-brown or grey-blue discoloration in a previously existing pale brown nevus is more characteristic to clonal nevi than the fried-egg appearance mentioned by Ball and Golitz.

Bologna and co-workers in 1994 also recognized the importance of eccentric hyperpigmented spots in nevi⁴. They found in 4 among their 59 cases the presence of deep dermal melanocytes and melanophages and these nevi were considered retrospectively as clonal nevi in 2004.

Huynh and co-workers³ mentioned that the correct clinical analysis makes possible the distinction of clonal nevi from the also rare so-called cockarde nevi with bull's-eye appearance.

The original immunohistochemical analysis of 18 clonal nevi showed¹ overall S100 protein positivity and in half of the cases they could detect abnormal p53 staining. However pathological p53 staining could be found apart from malignant melanoma even in banal nevi and other benign tumors⁵. The dermal nests of epithelioid melanocytes in clonal nevi show also HMB45 positive staining⁶.

Kazakov and co-workers⁷ in 2004 demonstrated that the presence of anti-MAGE antibody (B57) staining can be detected among benign melanocytic tumors most frequently in clonal and deep penetrating nevi. Because of this finding the above mentioned staining are also not suitable for differentiating between benign and malignant entities.

The biological behavior of clonal nevi biologically is benign. None of the lesions listed in the literature was followed by recurrence or metastasis even after years of excision. The removal of the whole lesion with free lateral margins is recommended.

The exact pathogenesis of clonal nevi is not known. Benign phenotypical alterations in a nevus are suspected or other authors draw a parallel with epigenetic features in combined nevi.⁸

2.1.2 Childhood melanoma

Approximately 1-3% of all childhood malignant tumors are melanomas and only 0.3-0.4% of all malignant melanomas arises in children under the age of 14. The precise incidence and prognosis of childhood malignant melanomas are not known although there are increasing numbers of literature data about this subject in the recent years⁹⁻¹⁹.

There can be several causes of this:

- definition of “childhood” varies in the literature: mainly the cases between 12 and 18 years of age are questionable
- prepubertal malignant melanomas are exceedingly rare even in the high-incidence Australia
- the prognostic factors are not similar in the earlier and recent publications
- the follow-up period in the recent literature is too short to assess the prognosis

Richardson and co-workers¹³ classified the prepubertal melanomas in three groups:

- congenital melanoma: the melanoma develops in the intrauterine life and is present at birth
- infantile melanoma: the tumor appear in the first year of life
- childhood melanoma: melanomas occurring from birth to 12 years of age

Statistical data also shows exponential increase in the incidence of melanoma around the age of 12²⁰.

They summarized the different risk factors in childhood melanomas as well: giant congenital nevi, dysplastic nevi, xeroderma pigmentosum, genetic immunodeficiency, or secondary immunosuppression (organ transplantation or HIV infection) can be found quite frequently in the background of these cases.

Congenital melanoma can develop through transplacental transmission if the mother suffers from malignant melanoma. Congenital melanoma can also arise as a dermal-subcutaneous node on the basis of a giant congenital nevus, and de novo cases could occur sometimes.

One third of childhood melanomas develops also on the basis of a giant congenital nevus and they develops relatively early during the first 5 years of life.

At the same time however so-called proliferative nodules can grow in these giant nevi in the neonatal period which ones can be extremely difficult to differentiate from melanomas both

clinically and histopathologically (7., 8., 9. patients). The presence of atypia and mitotic activity can help in the diagnosis ¹⁶. Consultation of several experienced pathologists is needed in such problematic cases. Close follow-up with careful photo documentation are necessary and this can help in the judgment of equivocal lesions.

Melanomas developing in small congenital nevi are mainly occurs after puberty. There is no consensus in the literature whether these nevi denotes increased risk for melanoma development.

Approximately half of childhood melanomas develop de novo and their clinical and histopathological appearance is similar to their adult counterparts.

In differential diagnostic point of view apart from the vascular lesions such as pyogenic granuloma or hemangiomas the differentiation a real childhood melanoma from Spitz' nevus can be very difficult both clinically and histopathologically ¹⁷.

Handfield –Jones and co-workers ¹¹ collected those histopathological features that can help to differentiate the questionable lesions. The presence of asymmetry, pagetoid spread, expansive growing, lack of maturation, mitotic activity and cytological atypia can point towards a malignant lesion however even these findings are not absolute criteria of malignancy. In 1999 Spatz and co-workers worked out a 0-11 score grading system dividing their 30 cases into low, intermediate and high risk groups. They classified tumors according to age of onset, size, presence or absence of ulceration, involvement of subcutis and mitotic activity and followed their patients for a 3 year period ²¹.

Treatment options in childhood melanoma cases are similar as in adult patients ^{17, 22}: surgical excision according to tumor thickness and sentinel node examination. The later is crucial for assessing exact staging. However radical regional lymph node dissection is controversial and should be decided upon individual considerations. In the case of a metastatic disease cytostatic or interferon treatment are recommended. In rare cases extremity perfusion or vaccination can be the treatment of choice.

2.1.3. Nevi and melanoma in tattoos

The dictates of fashion have led to a recent dramatic increase in the number of decorative tattoos being applied to the human body worldwide ²³⁻²⁶. Various dermatological diseases either inflammatory processes (contact dermatitis, granulomatous inflammation, or sarcoidosis), or infections (impetigo, tuberculosis, hepatitis B and C, or viral warts), or tumors may be caused by different tattooing agents. Keratoacanthoma, basal cell carcinoma and squamous cell carcinoma have been documented with some frequency in connection with a tattoo, but reports of melanoma in this respect are exceedingly rare ^{24,27,28}. Although the incidence of melanoma and the number of decorative tattoos have recently been increasing, tattoos are generally not considered as risk factors for melanoma formation ^{23,29}. As there have been only 13 previous cases in the literature ^{23,25,30-38} and the methods and materials of tattooing differ, it is impossible to prove a direct connection between tattooing and the malignant process ^{23,32,34,35}. Mere coincidence can be the possible explanation ^{23,34,35,38}, however according to the previous reports other associations could be considered. Ultraviolet light, photoallergic effect, inflammatory reaction or trauma may promote the malignant transformation ^{25,31,36}. The tattooing ink applied to denote a radiation field during the radiotherapy and the irradiation itself emerged to be co-carcinogens ³². It is also well known that the incidence of melanoma is increasing worldwide, as is the number of melanocytic lesions ^{23,29}. Accordingly, it is to be expected that dermatologists will in the future have to deal with increasing numbers of melanocytic lesions in association with tattoos.

Another interesting question is the management of melanocytic nevi localized in the tattoo area. To date the correlation of nevi and tattoos has not been studied ^{39,40}. Furthermore one must also consider that tattooing causes problems in the assessment of a sentinel node biopsy in a patient with malignant melanoma. As the tattoo pigment can mimic metastatic disease, it is very important for surgeons and pathologists to be informed in advance, as to whether the patient has a previous history of tattooing or tattoo removal ⁴¹⁻⁵³.

2.2. Rare non-melanocytic skin tumors

2.2.1. Merkel cell carcinoma

Merkel cell carcinoma (MCC) (a neuroendocrine carcinoma of the skin, trabecular carcinoma) is a rare but aggressive tumor that affects mostly elderly individuals of Caucasian origin. It usually develops on sun-damaged skin, particularly in the head and neck region⁵⁴. The tumor displays a high recurrence rate and regional spread that usually develops within 2 years after the first diagnosis. Similarly to Kaposi's sarcoma (KS), MCC occurs more frequently among immunosuppressed individuals and AIDS patients⁵⁵. An increase in the incidence of MCC has been reported in the last two decades^{56 57}.

The tumor arises from the Merkel cells of the epidermis and infiltrates the dermis and the subcutaneous fat. Trabecular, intermediate and small cell variants can be observed. The cells are basophilic and form trabecules, sheets or nodules. The mitotic activity is high and the invasion of the lymphatic channels and small vessels are often. Immunohistochemically tumor cells usually express CK20, NSE, EMA, ChrA.⁵⁴

The similarities between KS and MCC raise the possibility that MCC, like KS, may have an infectious origin.

Feng et al.^{58,59} recently isolated a new human polyomavirus which they named Merkel cell polyomavirus (MCV) from MCC by applying the digital transcriptome subtraction methodology; they obtained viral DNA by the digital transcriptome subtraction of RNA from MCC, and detected MCV sequences in 8 out of 10 MCCs. Accordingly they suggested that MCV has a role in the pathogenesis of MCC⁵⁸⁻⁶¹. There have subsequently been other reports⁶²⁻⁶⁴ of the presence of MCV in patients with MCC and these observations prompted us to investigate the presence of MCV DNA sequences in our MCC patients.

2.2.2. Neglected basal cell carcinomas

Tumors on the surface of the skin are generally visible and considered to be easily recognizable both for health-care professionals and for the patients themselves. However people with neglected advanced skin neoplasms are still encountered in dermatological practice in the 21st century⁶⁵. There can be numerous causes of the delay in the diagnosis: the person may fear the diagnosis and the treatment or become accustomed to the usually slowly-

growing tumor. Old age, a low social milieu and an inadequate hygienic culture may also be factors explaining why some people are not aware of the significance of a delayed diagnosis. Basal cell carcinoma (BCC) is the most common cutaneous tumor and one of the most frequent skin diseases observed by dermatologists^{66,67}. Most of these tumors arise in the head and neck area, particularly in the elderly, and usually grow slowly. The metastatic potential is very low and is mainly detected in association with aggressive or long-standing, large neglected tumors⁶⁶⁻⁶⁹. The characteristics of BCCs suggest that they might well be the “ideal candidates” for neglected tumors^{66,67,70}.

Another challenging question is the treatment of these advanced neoplasms. However treatment possibilities of ordinary BCCs can be numerous, the therapeutic solution of the neglected cases demands an individual multidisciplinary approach and teamwork. Reconstruction and a long-term follow-up are usually needed, and despite the choice of the best possible treatment modalities, a rather unfavorable prognosis and a high recurrence rate are to be anticipated.

3. Aims

Apart from the conventional, frequent forms of different skin tumors the recognition of the different rare variants are very important. The knowledge of their clinical and histopathological features is essential for the correct diagnosis. As these tumors can be seen only occasionally it is very important to collect them or follow the patients and analyze their data. In this way we can gain the sufficient knowledge in order to treat patients with these kinds of diseases properly. These are the main considerations that led us to analyze the rare entities. Our main aims were the followings:

3.1. To collect the unusual, rare melanocytic tumors and non-melanoma skin cancers:

- Clonal nevi
- Childhood melanoma
- Nevi and melanomas in tattoos
- Merkel cell carcinoma
- Neglected basal cell carcinomas

3.2. Characterize the clinical and the histopathological features and the prevalence of clonal nevi with the retrospective analysis of the histopathological records.

3.3. To describe the prevalence, the clinical and the histopathological features, the treatment modalities the follow-up data and the prognosis of childhood melanoma with the retrospective analysis of the last 30 years' histopathological records.

3.4. To evaluate the clinical and histopathological characteristics of nevi and melanomas arising in decorative tattoos.

3.5. To examine the prevalence of Merkel cell polyomavirus in the Merkel cell carcinomas of the Hungarian population.

3.6. To summarize the background, the histopathological features and treatment possibilities in neglected basal cell carcinomas.

4. Patients and methods

We examined retrospectively and prospectively the routine histopathological material of the Department of Dermatology and Allergology, Albert Szent-Györgyi Clinical Center, University of Szeged. This means the collection of various skin biopsies approximately 5.000 per a year. We analyzed the biopsies using routine hematoxylin-eosin staining, special stains and immunohistochemical methods. The melanocytic lesions were examined with S100 protein, HMB45, MelanA and Ki67 antibodies, the Merkel cell carcinomas with CK20, ChrA, EMA (DakoCytomation®) and NSE (Novocastra Laboratories®). When it was needed – in the case of Merkel cell carcinomas – molecular diagnostic tools were used.

4.1. Melanocytic tumors

4.1.1. Clonal nevi

With the systematic search of more than 4.000 surgical biopsies of year 2006 we found 8 clonal nevi among 1267 melanocytic nevi. The results are collected in Table 1.

4.1.2. Childhood melanoma

We collected the childhood melanoma cases which have been diagnosed during the last 30 years. Although the definition of childhood period is not uniform in the literature – as it was mentioned previously – we decided to consider a melanoma as a childhood one if the patient was between birth and 16 years of age.

We detected 14 cases in this period and the results are summarized in Table 2. This contains the patient's age and sex, the tumor's localization and histopathological parameters, the treatments and the follow-up data.

4.1.3. Nevi and melanoma in tattoos

We managed to diagnose two cases of dysplastic nevi and one of malignant melanoma in decorative tattoos. We also detected another melanoma case where we found tattoo pigment in the sentinel lymph node. The patient's melanoma in this case has not been in direct connection with a tattoo but the body area was the same.

4.2. Rare non-melanocytic skin tumors

4.2.1. Merkel cell carcinoma

We have examined 12 tumors from 10 patients with MCC (Table 3), selected retrospectively from the period between 2001 and 2010. We analyzed the biopsies using routine hematoxylin-eosin staining, immunohistochemical methods. MCCs typically stain positively with cytokeratin 20 (CK20), epithelial membrane antigen (EMA), chromogranin A (ChrA) and neuron specific enolase (NSE). Randomly selected paraffin-embedded samples of 13 squamous cell carcinomas, 10 basal cell carcinomas, 3 baso-squamous carcinomas and 3 malignant melanomas were used for comparative purposes. The study was approved by the Ethical Committee of Szeged University.

Preparation of clinical samples and isolation of the DNA content

Ten- μ m sections were obtained from formalin-fixed paraffin-embedded tissue biopsy specimens from the patients. The sections were extracted with xylene to remove paraffin, which was followed by two washes with absolute ethanol to remove the xylene. The ethanol was then evaporated off. DNA was extracted by proteolytic digestion with proteinase K (200 μ g/ml), the enzyme was then heat-inactivated and the low-speed supernatant was used directly for PCR analysis ⁷¹.

DNA amplification

The presence of MCV was detected by primer-directed amplification with PCR. Specific primer pairs were designed to detect the viral large T protein (LT1 and LT3), and the viral capsid protein (VP1) ^{58,59}. The following primer pairs were used: 5'-TAC-AAG-CAC-TCC-ACC-AAA-GC-3' and 5'-TCC-AAT-TAC-AGC-TGG-CCT-CT-3' for LT1 (439 bp), 5'-TTG-TCT-CGC-CAG-CAT-TGT-AG-3' and 5'-ATA-TAG-GGG-CCT-CGT-CAA-CC-3' for LT3 (308 bp), 5'-TTT-GCC-AGC-TTA-CAG-TGT-GG-3' and 5'-TGG-ATC-TAG-GCC-CTG-ATT-TT-3' for VP1 (351 bp). For the PCR amplification, a sensitive GoTaq® Flexi DNA polymerase system (Promega, Madison, USA) was used with 0.5 μ g/10 μ l genomic DNA, and 20 pmol of each primer.

To demonstrate that the quality and quantity of the DNA samples isolated from the formalin-fixed paraffin-embedded tissue biopsies were acceptable, a 268-bp segment of the human β -globin gene was also amplified ⁷².

Demonstration of amplimers

Amplification products were separated by electrophoresis in 1.5% agarose gel stained with GelRed (Biotium). For the DNA sequence analysis, the PCR products were excised from the gel under ultraviolet light and purified with the Cycle-Pure Mini Kit (OMEGA Bio-Tek Inc., Norcross, USA) according to the manufacturer's instruction. The purified PCR products were subjected by direct sequencing.

4.2.2. Neglected basal cell carcinomas

During the past 10 years, 5 neglected advanced cases of BCC were diagnosed in our regional center of dermatological oncology. The main clinical characteristics of the patients and the applied treatments are listed in Table 4.

Table 1.

The clinical data of patients with clonal nevi in 2006

Patient	Age/Sex	Localization	Size (mm)	Nevus color/shape	Hyperpigmentation			Clinical diagnosis
					location /	color /	size (mm)	
1.	28 ♀	chest	11x7	light brown, irregular	central	black	2	DN? in situ MM?
2.	17 ♂	scalp	4	brown	central	bluish	-	combined nevus
3.	33 ♂	abdomen	11x9	light brown	-	-	-	Nevus
4.	12 ♀	forearm	9x7	light brown	central	dark brown	2	Nevus
5.	22 ♀	forearm	5	light brown	central	brownish-black	2	DN? malignant transformation?
		thigh	3	brown	-	-	-	Nevus
6.	20 ♀	forearm	6	blue-grey	-	-	-	Nevus
7.	15 ♂	back	3	red-brown	eccentric	dark brown	1	DN

Table 2.

Clinical and histopathological characteristics and the follow-up data of childhood melanomas

Patient	Age at onset	Sex	Localization	Preexisting lesion	Histopathological diagnosis	Outcome / Follow-up
Congenital melanomas						
1.	2 days	♀	trunk	giant congenital nevus	no histology	lymphadenomegaly, alive 7 years lost for follow up
2.	6 days	♀	generalized	giant congenital nevus	NMM, pT2b, 1,216 mm	metastasis, lymphadenomegaly, without symptoms, alive 7 years
3.	5 days	♀	generalized	giant congenital nevus	malignant transformation? proliferative nodule?	lost for follow up
Childhood melanomas						
4.	5 y/o	♀	scalp	giant congenital nevus	NMM	metastasis deceased at age 9
5.	15 y/o	♀	back	nevus	NMM, 6mm	lymph node metastasis, deceased
6.	14 y/o	♂	back	nevus?	NMM	lost for follow up
7.	12 y/o	♂	upper arm	change in preexisting nevus	malignant transformation in a dysplastic nevus	without symptoms, dysplastic nevi, 6 years
8.	13 y/o	♂	back	dysplastic nevus	malignant transformation	without symptoms, 4 years
			back	dysplastic nevus	SSM, pT1a, 0,532mm	2 years
9.	15 y/o	♀	back	dysplastic nevus	malignant transformation, pT1a, 0,912 mm	without symptoms, 4 years
10.	13 y/o	♀	upper arm	dysplastic nevus	SSM, pT1a, 0,456 mm	without symptoms, 3 year
11.	11 y/o	♀	forearm	congenital nevus	spitzoid MM, pT3a, 2,28 mm	reexcision, negative SNB 2 years
De novo melanomas						
				clinical dg		
12.	14 y/o	♀	lower limb	Spitz?	NMM, pT4b, 5,396 mm	lymph node metastasis, without symptoms, 14 years
13.	14 y/o	♀	back	unknown	NMM, pT3b, 2,66 mm	alive, without symptoms, IFN, 9 years
14.	11 y/o	♀	back	Spitz?	NMM, pT3b, 3,04 mm	alive, without symptoms, IFN, 7 years

Table 3.

Clinical and immunohistochemical characteristics and MCV PCR results

Age: age at the time of the analyzed lesion's excision

Patient	Age/sex	Localization	Tumor type	IH	Human β -globin	LT1	LT3	VP1
1	85 / ♂ 86	cheek	primary (1/a)	ChrA + NSE +/-	+	-	+	-
			recurrent lesion (1/b)	ChrA + CK20 + EMA +	+	+	-	-
2	87 / ♀	forearm	upper recurrent lesion (2/a)	ChrA + CK20 +	+	+	+	-
			lower recurrent lesion (2/b)	ChrA + CK20 + EMA +	+	-	+	-
3	71 / ♂	forearm	2nd recurrent lesion	ChrA + CK20 + NSE +	+	-	+	-
4	57 / ♀	forehead	recurrent lesion	ChrA + CK20 -	+	-	-	-
5	79 / ♂	chest wall	primary	NSE +/- ChrA -	-	-	-	-
6	65 / ♂	nose	primary	ChrA +/- CK20 +/-	+	-	+	-
7	84 / ♀	nose	primary	ChrA + NSE +	+	+	+	+
8	76 / ♀	lower leg	primary	CK20 + EMA + ChrA +	+	(+)	+	(+)
9	64 / ♂	ankle	primary	CK20 + EMA + ChrA +	+	+	+	+
10	84 / ♀	left shin	primary	CK20 + ChrA +	+	+	+	-

Table 4.

The main clinical data of the neglected BCC patients and their treatment

Patient	Age/sex	Living place	Duration, clinical history	Diagnosis	Treatment
1.	44 y/o, male	farm	injury 2 years ago, growing lesion for 10 months	BCC	surgical removal
2.	96 y/o, female	town	more than two years	BCC	Radiotherapy
3.	63 y/o, male	town	several years, rapid growing for months	BCC with suppurative inflammation	surgical removal
4.	84 y/o, male	village	1 year	BCC	surgical removal
5.	68 y/o, male	village	1 year, immunosuppressed (renal transplant) patient	neck: BCC face, ear: SCC	surgical removal

5. Results and discussion

5.1. Rare melanocytic tumors

5.1.1. Clonal nevi

Clinically these nevi were presented as dark discoloration in an otherwise uniformly pigmented plaque. The newly developed dark area was the reason of surgical removal (Figure 1-2). The data of the nevi are presented in Table 1. This contains the size of the nevi and the size of the hyperpigmented area along with the clinical diagnosis. All lesions were diagnosed in adolescence or in young adulthood with the typical clinical presentation mentioned above. Two lesions clinically raised the possibility of malignant transformation one lesion was thought to be a combined nevus.

Histopathologically a compound melanocytic nevus could be seen with maturing nevus cell nests. Large epithelioid groups of melanocytes could be detected in the upper dermal part of the nevi. Sometimes the cells showed vacuolization. There was no considerable atypia or mitotic activity. Melanophages were situated around these foci. With immunohistochemical analysis the nevi showed overall S100 protein positivity. The junctional nevus cells and the epithelioid dermal melanocytes stained positively with HMB45 (Figure 3).

The typical clinical history and presentation along with the characteristic microscopic features helps to differentiate benign clonal nevi from malignant melanomas.

Figure 1/A:



Figure 1/B:



Figure 1/C:



Light brown nevi with central brownish-black pigmentation.

A: chest of Patient 1/Table 1

B: forearm of Patient 4/Table 1

C: forearm of Patient 5/Table 1.

Figure 2/A:

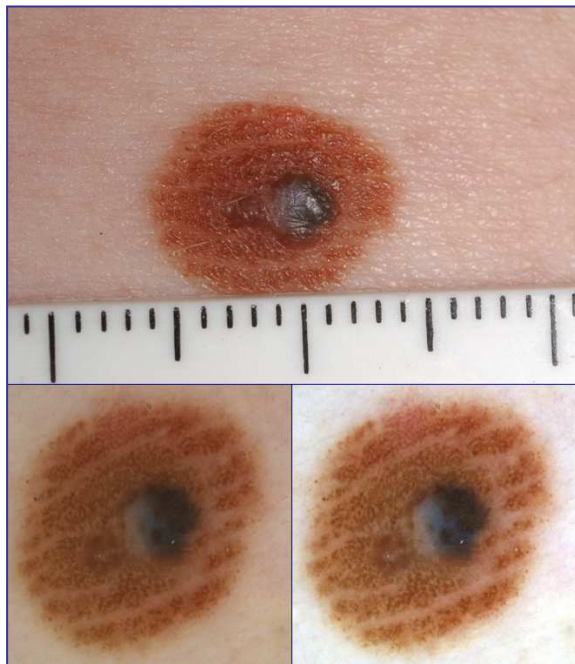


Figure 2/B:



The typical clinical appearance of clonal nevi and their dermoscopic picture (DermaGeniusUltra®) on the trunk of a 16-year-old male (A) and on the back of a 20-year-old female (B) patient

Figure 3/A:

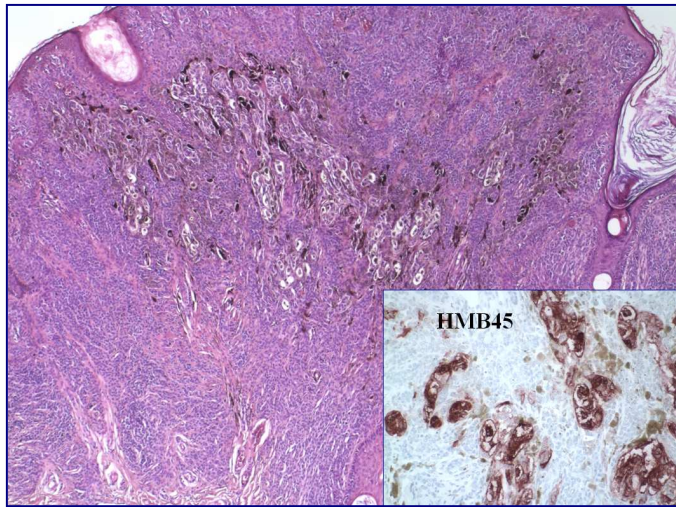


Figure 3/B:

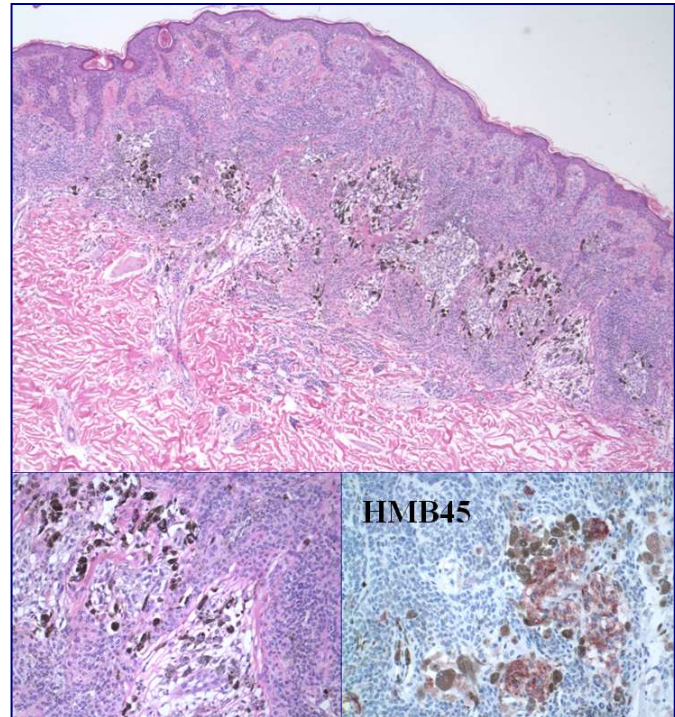
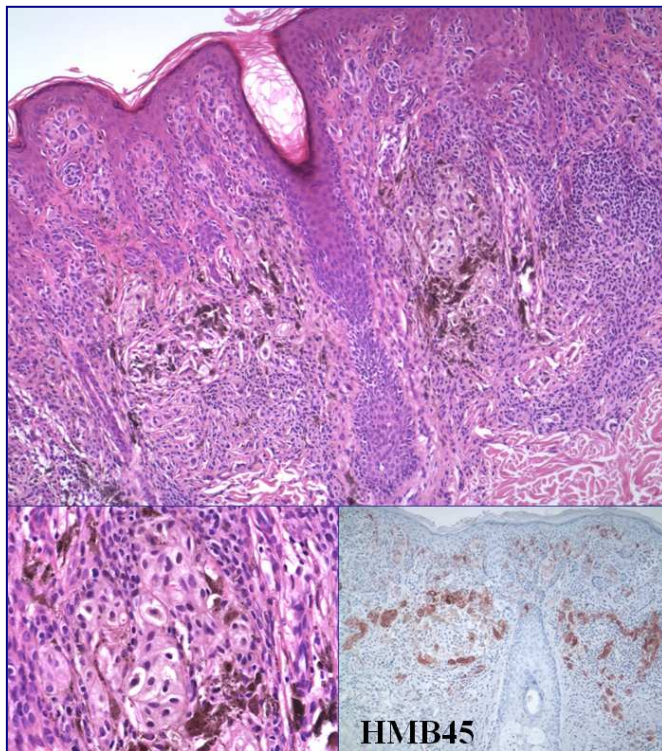


Figure 3/C



Compound melanocytic nevus with large epithelioid groups of melanocytes in the dermal part. These foci are HMB45 positive and pigment containing melanophages situated around them.

A: Patient 3/Table 1

B: Patient 5/Table 1

C: Patient 6/Table 1.

5.1.2. Childhood melanoma

We analyzed the data of 14 melanoma patients younger than 16 years of age. Three of these cases were sent to our histopathological laboratory as a consultation case.

There was female predominance, the female : male ratio was 11 : 3.

Three patients were newborns, according to Richardson's classification¹³ and they had congenital melanoma. All these cases developed in giant congenital nevus (Figure 4-5). One newborn's parents did not agree in diagnostic biopsy. In case 3 histopathology suggested both the possibility of early malignant transformation and presence of proliferative nodule (Figure 5). Surgical excision and close follow up was performed in these newborn patients.

All of the other 11 patients had childhood melanoma. 8 of these neoplasms developed on the basis of a preexisting melanocytic lesion and 3 tumors appeared de novo. One girl was 5 years old at the time of the diagnosis (Figure 6), the other patients were older than 10 years of age. One tumor developed on the scalp (Figure 6), 7 on the back 3 on the upper and 1 on the lower extremity. (Table 2)

There was no history of genetic alteration or immunosuppression in our patients and the family history of melanoma was also negative.

Apart from the suspicion of malignant melanoma clinically Spitz' nevus and hemangioma emerged as differential diagnostic possibilities.

Histopathology revealed thick nodular melanoma in 7 cases (Figure 7). Patient 8 with dysplastic nevus syndrome has had double melanoma on the basis of dysplastic nevi (Figure 8). In cases with diagnostic difficulties (2., 3., 9. cases) we also took consultation help of other histopathologists.

During the follow up periods which lasts from 2 to 14 years two of our patient deceased due to the melanoma. One of them (Patient 6) had a special type, so called pigment synthesizing or animal type malignant melanoma (Figure 9). Patient 2 with giant congenital nevi developed a subcutaneous metastasis which was removed. There was no patient with local recurrent disease but regional lymph node involvement could be detected in 2 cases (Figure 10). Two patients received interferon treatment. Three other patients were lost for follow-up.

The diagnosis of melanoma in a child is difficult both for the clinician and the histopathologist. Very careful analysis of the histopathology material, consultation with experienced pathologists is always necessary in order to differentiate these lesions from other childhood melanocytic lesions¹⁷.

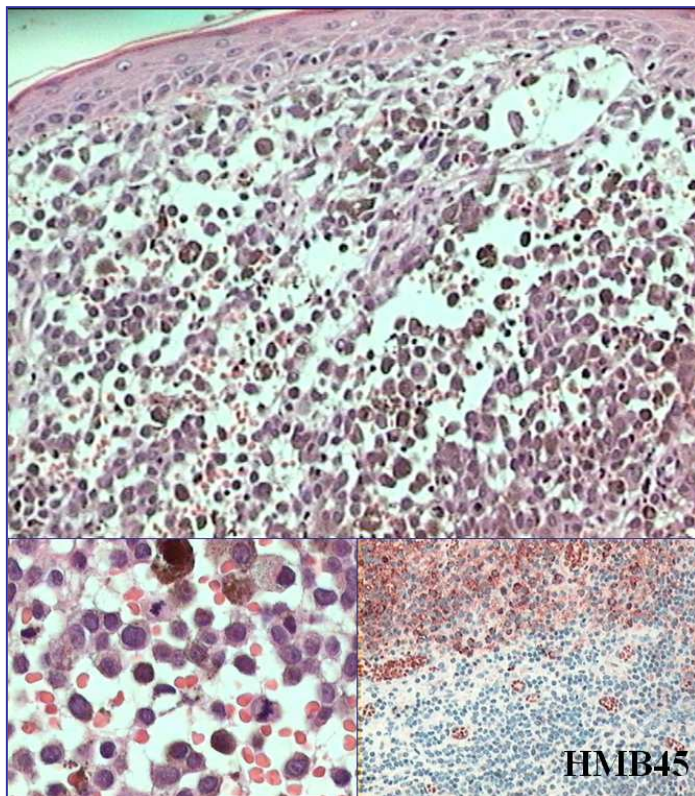
Figure 4/A.:



Patient 2/Table 2 with giant congenital nevus after birth and at age 3.



Figure 4/B:



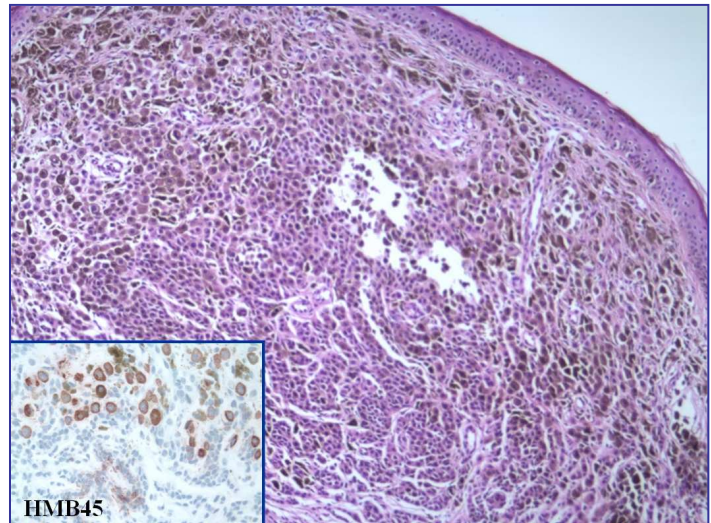
Patient 2/Table 2: Congenital malignant melanoma within the giant congenital nevus. Mitotic figures could be seen on the high power picture. The malignant part shows HMB45 positivity.

Figure 5/A:



Giant congenital nevus

Figure 5/B:



The possibility of early malignant transformation and the presence of proliferative nodule also emerged with the histopathological examination. Patient 3/Table 2.

Figure 6:



The scalp lesion of Patient 4/Table 2

Figure 7:
Spitzoid malignant melanoma (pT3a)
on the basis of a congenital nevus
on the forearm of Patient 11/Table 2.

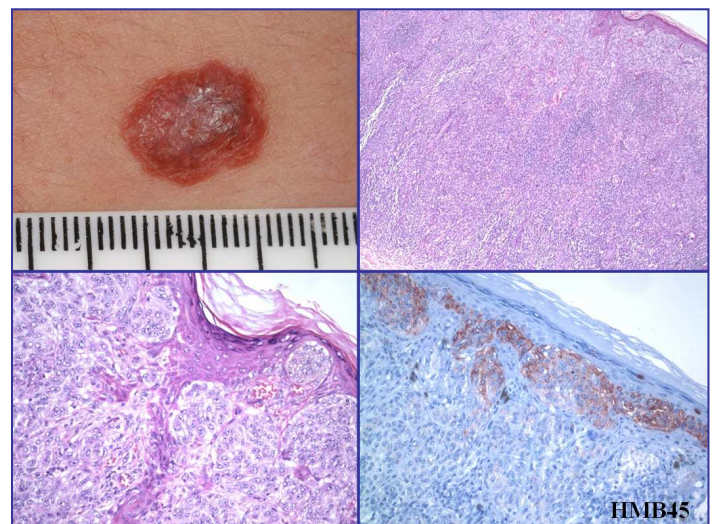
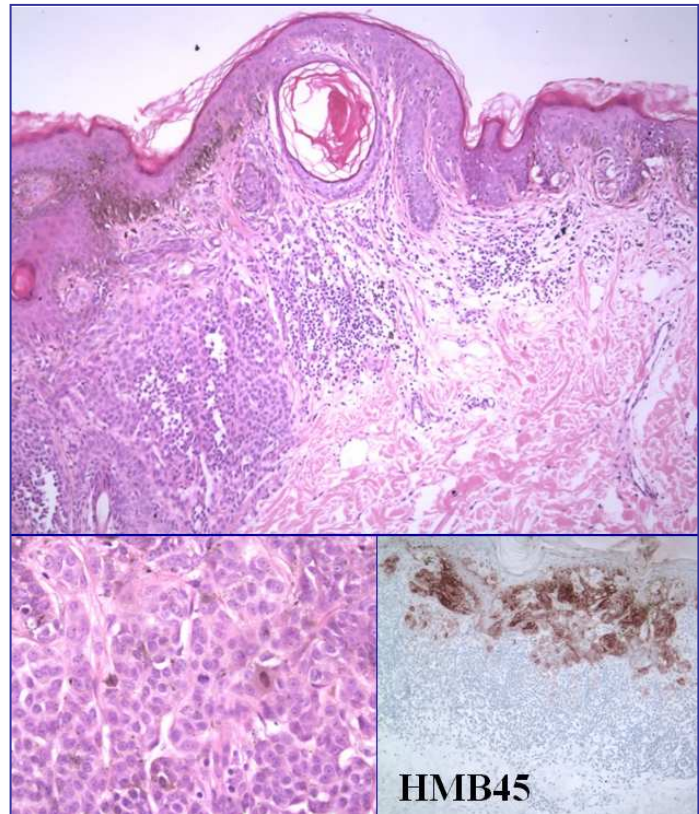
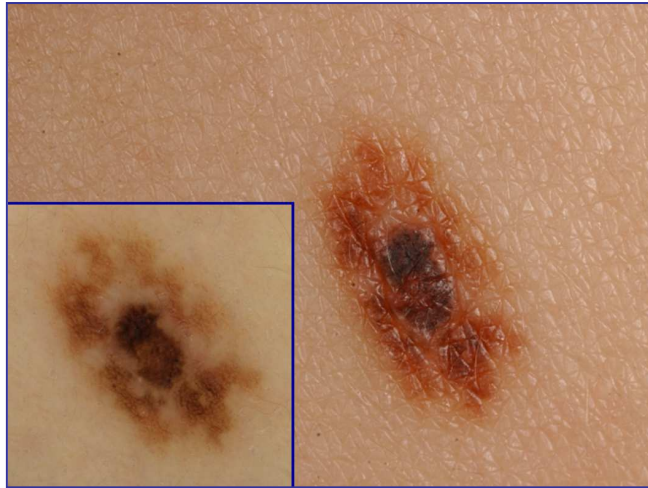
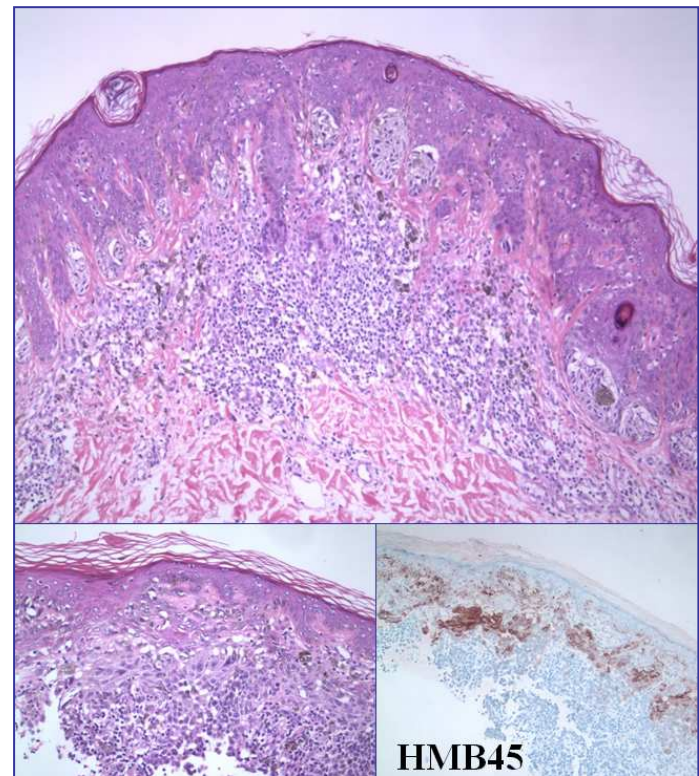


Figure 8/A:



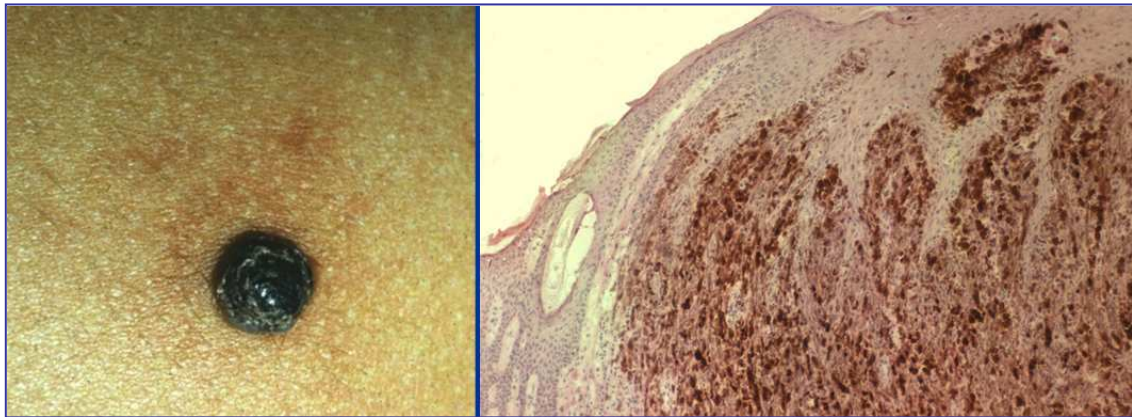
The 1st lesion of Patient 8/Table 2: malignant transformation in a dysplastic nevus.

Figure 8/B:



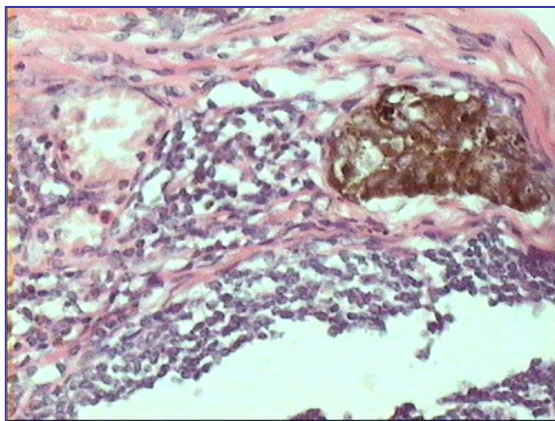
The 2nd lesion of Patient 8/Table 2: superficial spreading malignant melanoma, pT1a

Figure 9:



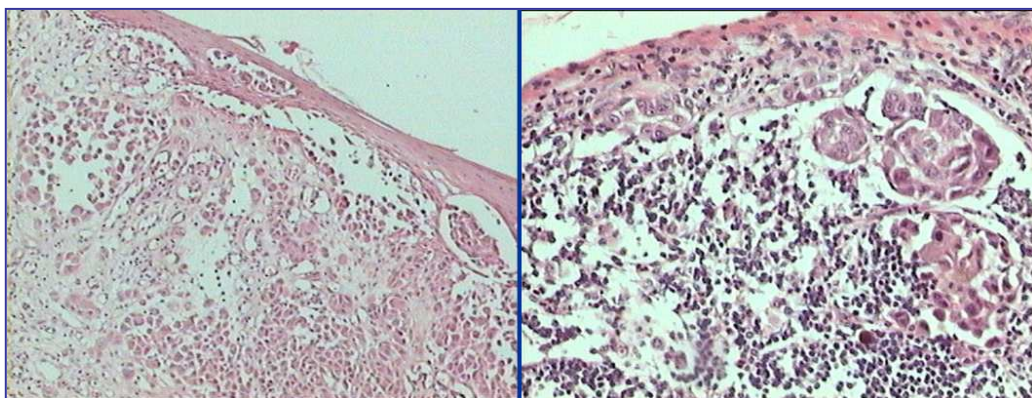
The so-called pigment synthesizing or animal type malignant melanoma of Patient 6/Table 2. The tumor cells contain large amount of melanin.

Figure 10/A:



The lymph node metastasis of Patient 5/Table 2.

Figure 10/B:



The primary tumor and its lymph node metastasis of Patient 12/Table 2.

5.1.3. Nevi and melanoma in tattoos

Case reports

Patient 1

A 28-year-old Caucasian male had had a mole on his left upper arm since childhood. A non-figurative tattoo was placed on that site approximately 5 years earlier at his age of 23. The extensive tattoo covered the right upper aspect of the back, the right shoulder and the right upper arm down to the elbow. The tattooing on the arm consisted of black lines. He suffered an injury to the mole at his age of 27 and since then the lesion has gradually become larger and crusted. Otherwise, he presented in good health, with numerous nevi and lentiginos even in the tattoo itself. Clinical examination revealed an erythematous and brown, polychromatic, markedly asymmetrical, slightly raised plaque 13 x 15 mm in maximal dimension with irregular borders, and signs suggestive of regression on the left upper arm. The dermatoscopic picture (DermogeniusUltra®) demonstrated an atypical pigment network and grayish-blue areas (Fig. 11). The clinical diagnosis was malignant melanoma and the lesion was removed surgically with 0.5 cm margins. The histopathology confirmed the clinical diagnosis. The tumor was a melanoma, superficial spreading type with a small ulceration and parakeratosis on the surface and with a remnant of the previous nevus (Figure 12). The mitotic count was 2 mitosis / mm². The Breslow thickness was 0.99 mm, and invasion to Clark level II was detected. According to both the 2001 and 2009 recommendations of the AJCC for staging of cutaneous melanoma the tumor was classified pT1b. The tumor cells exhibited diffuse positivity with S100 protein and focal positivity with HMB45 and MelanA reactions (Figure 13). Around the lesion, black tattoo pigment could be seen perivascularly and among collagen bundles. In view of the clinical data and the histopathology, reexcision with 1 cm safety borders and sentinel lymph node biopsy were performed. There was no tumor remnant in the skin or metastatic lesion in the lymph node. However, the lymph node contained a large amount of black tattoo pigment (Figure 13). The staging examinations (chest X-ray, abdominal ultrasound, cranial CT and bone scan) were all normal and the serum LDH level was in the normal range. The patient is under regular follow-up and he has been symptom free for five years.

Patient 2

A 34-year-old Caucasian male had an injured mole on his right upper arm in a decorative non-figurative black tattoo. The tattoo which was approximately 20x10 cm covered almost the whole lateral aspect of the upper arm. The tattoo was applied 5 years earlier at his age of 29 and the mole enlarged within the last two years. The clinical diagnosis was “injured

melanocytic nevus”. Histopathology revealed a severely atypical dysplastic junctional melanocytic nevus. Ulceration on the surface, fresh hemorrhage and an acute inflammatory cell infiltrate could be seen in the nevus (Figure 14). In the dermis, black tattoo pigment could be detected. As the nevus reached one of the resection margins, reexcision was carried out. No signs of residual nevus were found; only scar tissue was detected. The patient has a hypertrophic scar on his arm and he is symptom free.

Patient 3

A 23-year-old Caucasian female presented with a large, artistic, multicolored decorative tattoo on her lumbar region (Figure 15). She had previously had a few moles in that area. The patient had not observed any major changes, but on clinical examination one of these moles raised the suspicion of malignant melanoma. This lesion was 7x5 mm in maximal dimension, an asymmetrical, slightly raised plaque with grayish-brown pigmentation and with irregular borders in a field of red and blue tattooing (Figure 15). The lesion was excised with 0.5 cm margins. The histopathology revealed a lentiginous moderately dysplastic compound melanocytic nevus. In the dermis, tattoo pigment could be detected in macrophages and among collagen bundles (Figure 16). Immunohistochemically, the melanocytic cells were diffusely positive with S100. The HMB45 reaction was positive in the melanocytes at the dermoepidermal junction and in only some cells in the papillary dermis.

Patient 4.

A 22-year-old Caucasian female had had a black mole on her back below the left scapula since she could recall. The mole enlarged rapidly in a few months and its color became bluish without any injury. The clinical examination raised the possibility of a malignant melanoma or a vascular neoplasm. The tumor was removed with 0.5 cm margins. The histopathology revealed an exophytic, spitzoid ulcerated nodular malignant melanoma which invaded the dermis only to Clark level II but the Breslow thickness was 2.43 mm, pT2b (Figure 17). The tumor cells stained diffusely with S100 protein, MelanA and HMB45 with immunohistochemistry. The Ki67 reaction showed 30% proliferation rate (Figure 18). Reexcision with 2 cm safety borders and sentinel lymph node biopsy were performed. During the operation 3 lymph nodes were removed. One of the nodes situated on the chest wall, the two others were in the left axilla. The first lymph node contained scattered MelanA and HMB45 positive tumor cells (Figure 19). One of the lymph node from the axilla did not show any metastatic disease however contained quite large amount of black pigment (Figure 20). A few tumor cells and just some black pigment also could be found in the other axillary lymph node. As the black pigment histopathologically looked as an exogenous one the possibility of

tattoo pigment had been suggested. The clinical examination confirmed the presence of a yellow-black tattoo on the patient's wrist (Figure 21). This tattoo was the origin of the black pigment in the lymph nodes. The subsequently performed regional lymph node dissection showed some more tattoo pigment and only a few tumor cells. The staging examinations (chest X-ray, abdominal ultrasound, cranial CT and bone scan) were all normal and the serum LDH level was in the normal range. The patient is on IFN treatment with regular follow-up and she has been symptom free for 9 months.

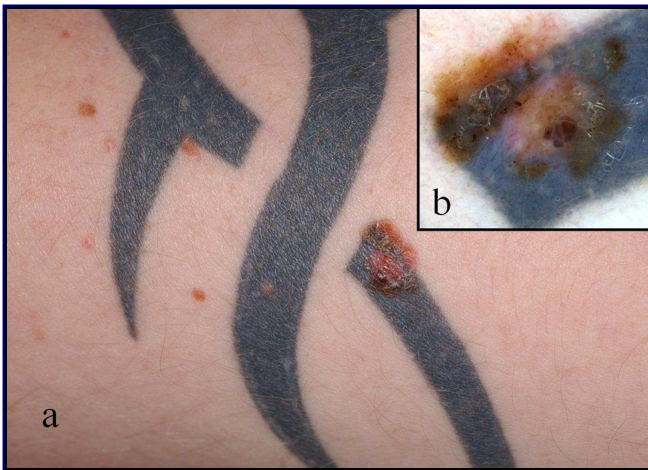
At present, the pathogenesis of melanoma developing in a tattoo is unknown. Mere coincidence cannot be ruled out however trauma, ultraviolet light, a photoallergic effect, or an inflammatory reaction may promote the malignant transformation. We diagnosed two cases of dysplastic nevi and one of malignant melanoma in decorative tattoos. With this we present the 14th case of a melanoma developing in a preexisting tattoo in the English literature.

As the 14th melanoma reported in a tattoo, our case exhibits numerous similarities with the previous ones. There had been a previous nevus at the site, and thus the possible effect of injury cannot be excluded. In our presented case, the tumor developed some years after the tattooing, though, the time interval was relatively short (5 years). In the previous cases reported in the literature melanoma developed 2 to 40 years after tattooing and 8 cases emerged even after 10 years or more (median interval 15,6 years). The main characteristics and clinical data of the previous cases and our melanoma case are listed in Table 5.

Another interesting question is the management of melanocytic nevi localized in the tattoo area. Dermatologists and histopathologists must be aware that the tattoo pigment can disguise changes in preexisting nevi when making clinical and histopathological diagnosis in these cases. To date the correlation of nevi and tattoos has not been studied^{39,40}.

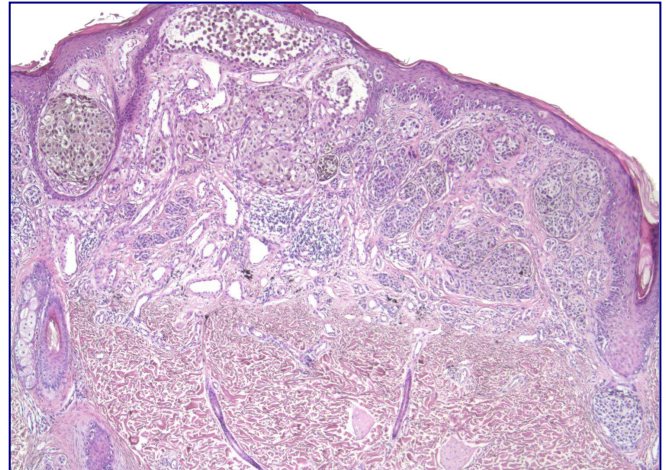
Furthermore one must also consider that tattooing causes problems in the assessment of a sentinel node biopsy in a patient with malignant melanoma. The tattoo pigment can cause the black discoloration of the sentinel nodes and other lymph nodes in the region, mimicking metastatic disease. Moreover, the black pigment can cause difficulties for the histopathologist in the detection of real metastatic cells. As the tattoo pigment can mimic metastatic disease, it is very important for surgeons and pathologists to be informed in advance, as to whether the patient has a previous history of tattooing or tattoo removal⁴¹⁻⁵³.

Figure 11:



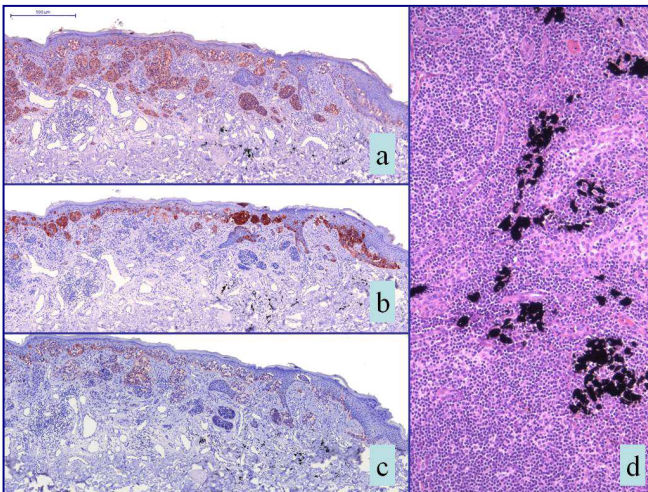
Patient 1: a) A brown, polychromatic, asymmetric, slightly raised plaque within a black tattoo and b) the dermoscopic picture.

Figure 12:



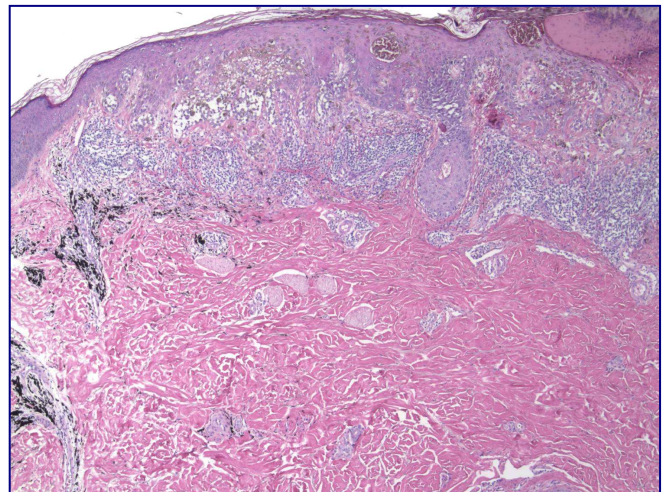
Patient 1: Superficial spreading melanoma in a previous nevus with tattoo pigment (HE, original magnification 5x)

Figure 13:



Patient 1: Tattoo pigment and tumor cells with a) S100 protein, b) HMB45 and c) MelanA d) Tattoo pigment in sentinel lymph node HE

Figure 14:



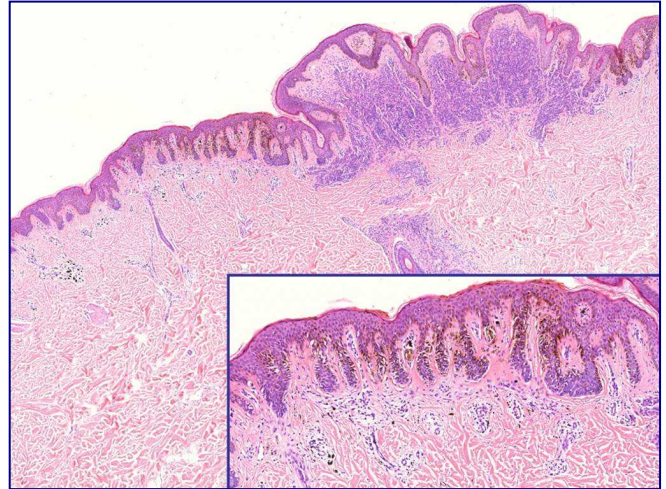
Patient 2: The inflamed, injured part of a severely atypical dysplastic nevus adjacent to tattoo pigment HE

Figure 15:



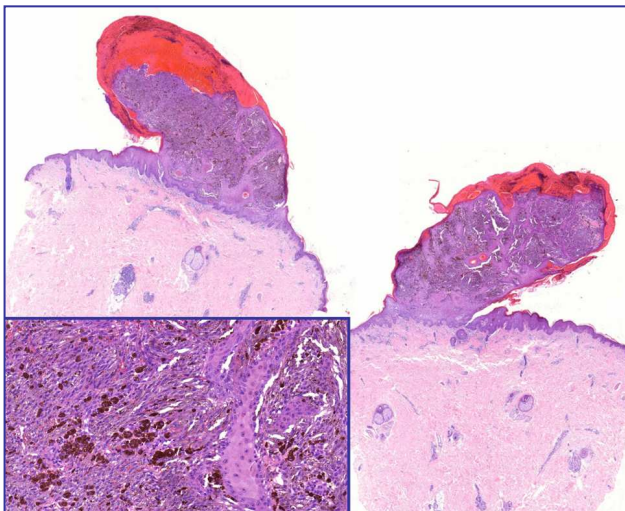
Patient 3: An irregular, slightly raised brown plaque in a multicolored tattoo

Figure 16:



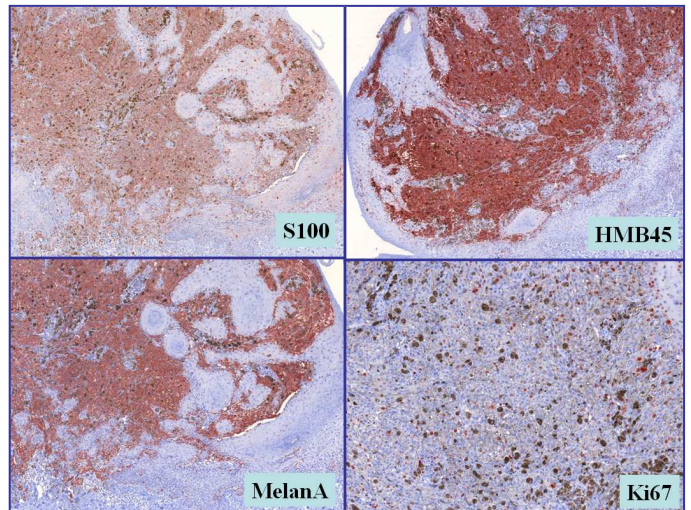
Patient 3.: The low-power view of the congenital compound nevus and the lentiginous moderately dysplastic lateral border of the lesion (insert) with tattoo pigment in the nearby dermis HE

Figure 17:



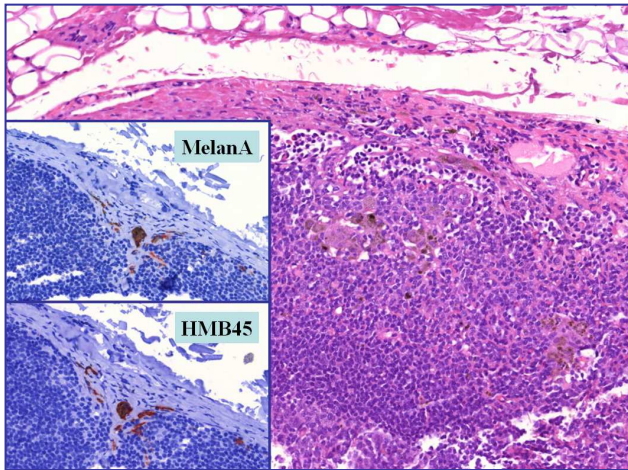
Patient 4.: An exophytic, spitzoid ulcerated nodular malignant melanoma (pT2b).

Figure 18:



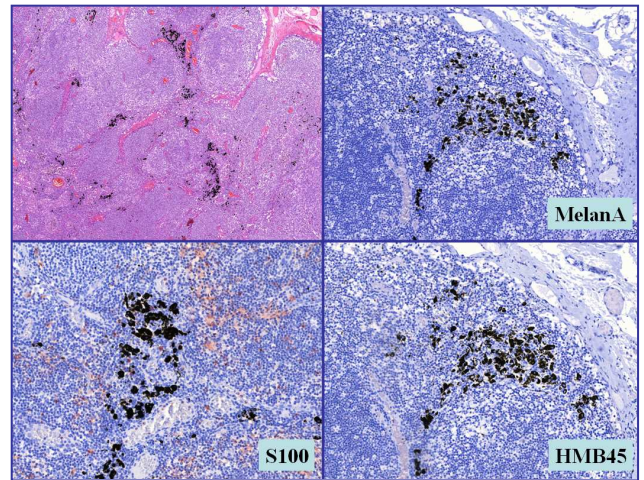
Patient 4: The tumor cells stained diffusely with S100 protein, MelanA and HMB45. The Ki67 reaction showed 30% proliferation rate.

Figure 19.



Patient 4.: The first lymph node contained scattered MelanA and HMB45 positive tumor cells.

Figure 20.



Patient 4.: One lymph node of the axilla did not show any metastatic disease however contained large amount of black tattoo pigment.

Figure 21.



Patient 4.: The site of the primary tumor on the left side of the back and the tattoo on the left wrist of the patient.

Table 5 helye!

5.2. Rare non-melanocytic skin tumors

5.2.1. Merkel cell carcinoma

Among the analyzed 10 cases the men:women ratio was 5:5, and the mean age at the time of the diagnosis of the primary tumor was 75,2 years. The youngest patient was 57 and the oldest was 87 years old; both were women. 7 tumors were primary and 5 were locally recurrent lesions. Three of the neoplasms had recurred after one year. In Patient 3, two recurrent lesions developed after 11 and 12 years. (Figure 22). Only Patient 2 had a previous history of endometrial carcinoma and irradiation therapy, 6 years prior to the MCC. Hypertension, arteriosclerosis, ischemic heart disease, pernicious anemia and NIDDM were each found in one or more patients.

The results of immunohistochemistry showed that the majority of the tumors stained positively with CK20 (8 tumors) and ChrA (11 tumors). (Table 3, Figure 23)

Of the 12 MCC tumors, 10 tested positive for MCV sequences by PCR (Table 3, Figure 24). One DNA isolate (patient 5) was negative for human β -globin PCR. Ten tumors were positive for LT1 and/or LT3 amplification, whereas only 3 tumors were positive for VP1. The amplified PCR products were retrieved from the bands and subjected to DNA sequence analysis. The results proved that the sequences of the amplimers were exactly the same as determined by each of the primer pairs in the MCV genome (Accession No. EU375803). We could not detect the presence of MCV DNA in our reference samples by using LT1, LT3 and VP1 primer pairs.

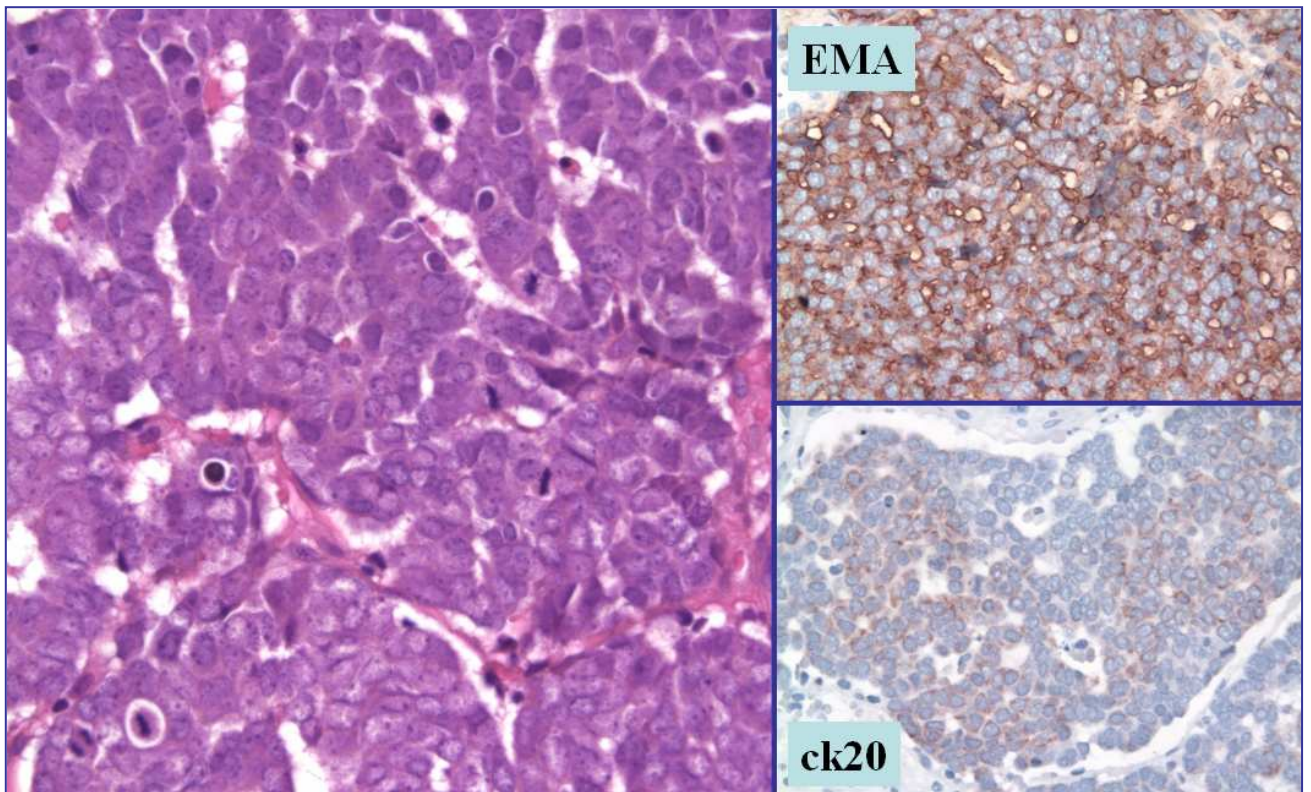
Thus, with MCV specific primers, we demonstrated the presence of viral T antigen and/or viral capsid DNA sequences in 10 of the 12 MCC lesions both in primary tumors and in recurrent lesions. Our results are very similar to those of Feng et al ^{58,59}. In the reference samples, originating from other skin malignancies (squamous cell carcinoma, basal cell carcinoma, etc.), we did not detect MCV DNA at all. MCV infection therefore seems to be specific for MCC. Our findings strongly support the hypothesis that MCV plays a role in the pathogenesis of MCC ⁵⁸⁻⁶¹.

Figure 22:



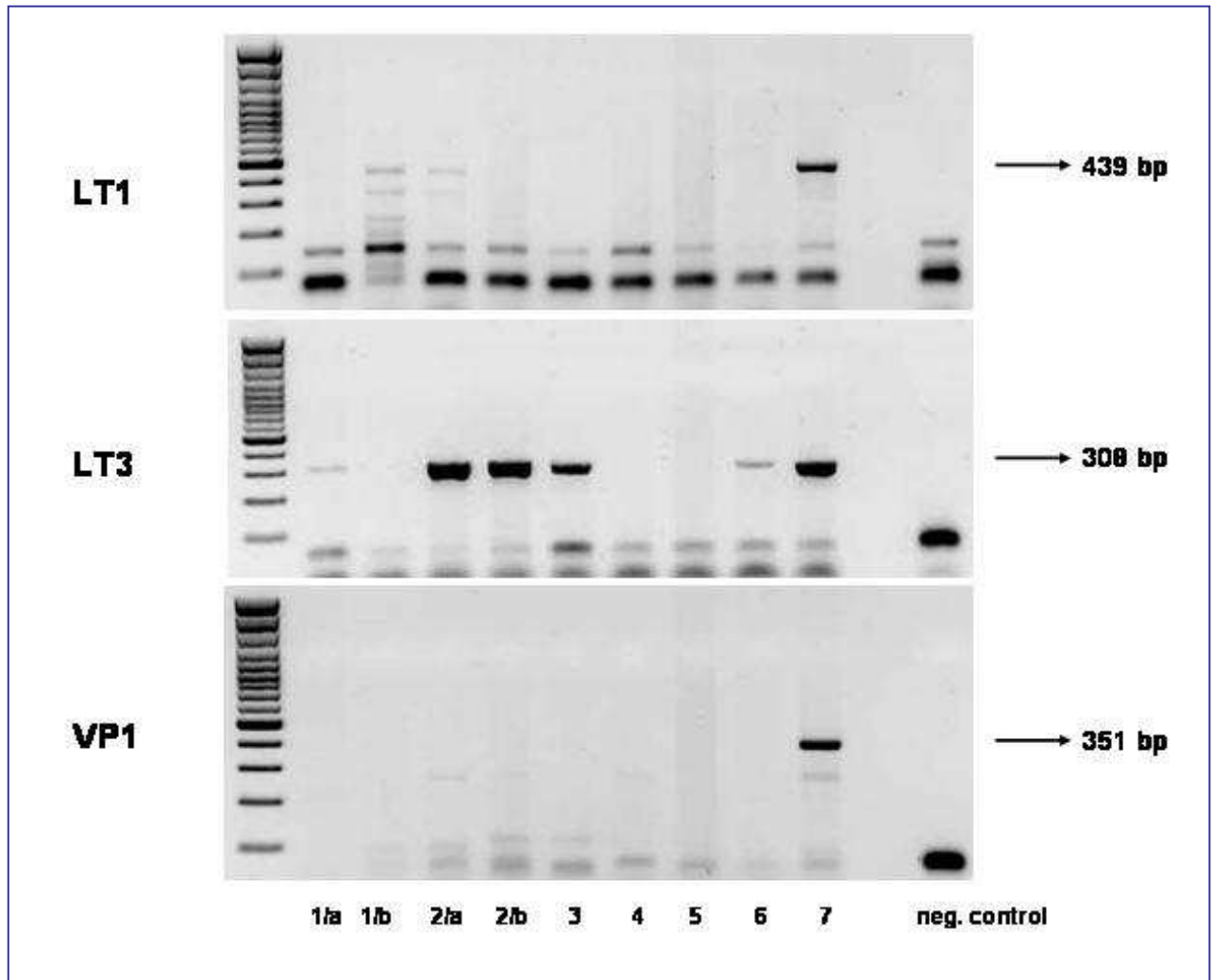
A: Patient 7/Table 3, primary Merkel cell carcinoma on the nose.
B: Patient 1/Table 3, locally recurrent tumor on the face.

Figure 23:



Patient 2/Tabl 3, Merkel cell carcinoma histopathology with HE, EMA and CK20 stainings.

Figure 24.



Amplification of the fragments of viral LT1, LT3 and VP1 genes using gene-specific primers. The resulting 439, 308 and 351 base pair fragments are visualized by GelRed (Biotium)-stained agarose gel electrophoresis.

Lane numbers correspond to the numbers of the samples in the first 7 patient of Table 3.

Lane 5: serves as control, from an MCC DNA isolate, the quality of DNA was insufficient (human β -globin PCR negative).

5.2.2. Neglected basal cell carcinomas

Case reports

Patient 1

When a 44-year-old male first sought for medical advice in December 2009 he had already had a mutilating, horrifying tumor on the right side of his face for 10 months. He lived alone in a farmhouse in a rural, but quite densely populated area. Two years previously, his own dog had clawed on the right side of the patient's nose, the injury leaving a scar. 11 months before his presentation he had suffered another minor injury in the same region caused by a splinter of wood. A gradually-growing, ulcerating lesion had subsequently developed on his face (Figure 25). The clinical diagnosis was BCC, but the possibility of Wegener's granulomatosis also emerged together with a suspicion of leprosy or some other bacterial infection. The CT scan revealed an extensive bone defect: the maxillary sinus had perished, half of the nasal bone and the zygomatic arch were missing and the external wall of the frontal sinus was involved. As three types of bacteria were identified, intravenous antibiotic treatment was started. Multiple biopsies confirmed the presence of BCC (Figure 26). The tumor was resected at the Oral and Maxillofacial Surgery Department and the defect was covered with a fronto-temporal rotation flap and a latissimus dorsi musculo-cutaneous free flap. In the postoperative period, the patient suffered a right-sided temporal lobe emollition of the brain, resulting in left-sided hemiplegia. The skin layer of the flap necrotized, but the muscular layer remained intact, and healed by secondary epithelialization. After 6 months, recurrences around the mouth necessitated repeated excisions with a forearm fascio-cutaneous free flap reconstruction. This flap necrotized in full thickness and it had to be removed, and the defect was closed in a direct manner. The patient is now tumor-free, but his face has not been reconstructed functionally or esthetically (Figure 27). His nutrition is solved, and physiotherapy has led to a significant improvement in his extremity movements: he can walk alone and use his left hand.

Patient 2

A 96-year-old female, living in a small town, presented in November 2007 with a 2-year history of a growing tumorous mass in the right inguinal region. The tumor was removed and the histopathology confirmed the presence of squamous cell carcinoma (SCC). At the same time, an ulcerated tumor on the right parieto-occipital region of her head was diagnosed clinically as BCC. Excision or irradiation therapy was planned after the removal of the inguinal tumor, but the patient did not continue the treatment. In 2009, she received neurosurgical treatment and was then referred to dermatology because of her growing cranial

tumor (Figure 28). An incisional biopsy from this tumor confirmed the diagnosis of BCC. In view of her age and the size and extent of the tumor, the multidisciplinary oncology team decided on irradiation therapy. This caused the tumor to regress, leaving an ulcer with visible bone at the base. In the meantime, the SCC recurred in the left groin lymph nodes, but no other dissemination was detected and the tumor mass remained stable for several months.

Patient 3

A 63-year old man living in an agricultural town had had a small exophytic skin-colored nodule in the middle of his back for many years. This had started to grow rapidly and become ulcerated during the past few months. By his first medical visit in September 2009, suppurative inflammation with abscess formation had developed in the nearby dermis (Figure 29). Consequently an incisional biopsy and incision of the abscess were initially performed, and systemic antibiotic therapy was administered. The histopathological diagnosis was BCC. Laboratory tests revealed that the patient had previously unrecognized non-insulin-dependent diabetes mellitus. In a second operation, the whole tumor was removed with conservative wound care because of the inflammation. The patient at first participated in regular surgical follow-up and treatment of the remaining ulcer, but he later failed to appear for the oncology follow-up.

Patient 4

An 84-year-old male resident in an agricultural village presented in September 2008 with numerous actinic keratoses on his head and neck, and with a slowly-growing tumorous mass in the presternal area, which he had observed one year previously (Figure 30). The tumor which proved to be a BCC, was removed with free a surgical margin and the defect was covered by a mesh-graft skin transplant. At the same time, an in situ superficially spreading malignant melanoma in a melanocytic nevus was removed from his back. The patient has currently been under regular follow-up for 2 years.

Patient 5

A 68-year-old male, living in a village, underwent renal transplantation in 1995 and had subsequently received immunosuppressive therapy. A slowly-growing tumor developed on the right side of his neck one year prior to his clinical presentation in 2009. Both the clinical and the histopathological diagnosis indicated BCC. Additionally, there were two small SCCs in the preauricular region and on the right ear (Figure 31).

There can be numerous reasons for delay in seeking medical advice. The factors are best documented in malignant melanoma cases ⁷³⁻⁷⁵ but non-melanoma skin cancers and

mesenchymal tumors⁷⁶⁻⁸⁰ are also seen in neglected forms from time to time. A low social milieu, inadequate hygienic culture associated with poverty and a low level of knowledge about skin tumors may be the explanation in some cases. Patients in these circumstances may not be aware of the possible significance of their growing lesion, though most of our patients live in towns or villages where family members, family doctors or neighbors are easily accessible and media campaigns can reach them. Old age and a slowly-growing, not painful neoplasm may also result in a delay in seeking medical advice. The patients may not see properly or not realize the changing and extremely unpleasant clinical picture or they might accept the slowly, but continuously progressing situation. Finally a delay may be caused by an incorrect initial diagnosis, although this occurs mainly with melanocytic tumors⁷³. The organ transplanted and/or immunocompromised individuals comprise a special group. In consequence of the immunosuppression, skin tumors are more frequent and more rapidly growing in these individuals.

It is interesting, that although the patients themselves are more or less aware of the growing tumor, it is usually some external event that finally impels them to seek medical advice, e.g. a sudden change in the lesion (bleeding or sudden growth) or encouragement by another person (a family member or friend)^{66-68,73,74}. A media campaign or a news article may sometimes stimulate a person to visit a physician⁷³⁻⁷⁵.

Another challenging question is the treatment of these advanced neoplasms. Numerous possibilities are available for ordinary BCCs: surgical excision, Mohs micrographic surgery, PDT therapy, cryosurgery, immunotherapy and radiotherapy are the most frequently used techniques^{66,68}. The therapy of neglected cases, however, demands an individual multidisciplinary approach and teamwork. The treatment of choice is often surgery (plastic, cranio-facial or neurosurgery) alone or combined with radiotherapy, with the help of imaging techniques (CT, MRI and angiography). Reconstruction and a long-term follow-up are usually needed, with the cooperation of medical experts. Despite the choice of the best possible treatment modalities, a rather unfavorable prognosis and a high recurrence rate are to be anticipated.

Figure 25:



Patient 1/Table 4: The mutilating tumor on the right side of the patient's face. By courtesy of Z. Raskó, Department of Oral and Maxillofacial Surgery

Figure 26:

Patient 1/Table 4: The first biopsy specimen shows the infiltrating BCC.

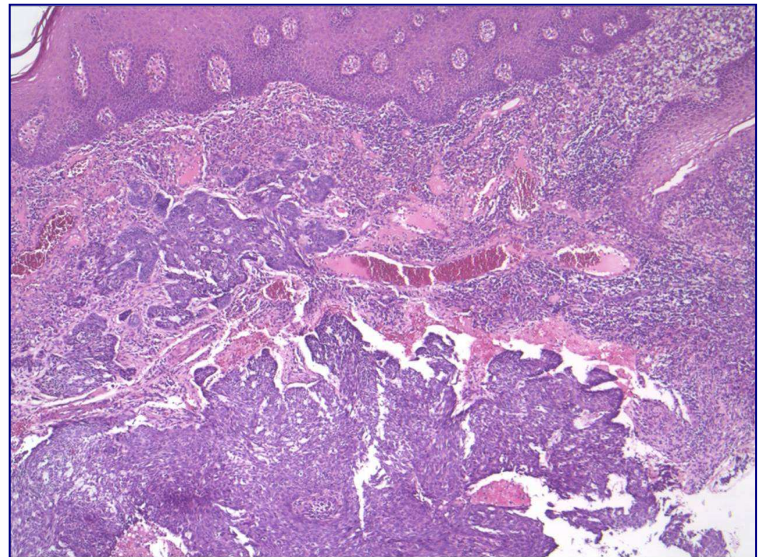


Figure 27:



Patient 1/Table 4: The patient is tumor free however his face is not reconstructed functionally and aesthetically. By courtesy of Z. Raskó, Department of Oral and Maxillofacial Surgery

Figure 28:



Patient 2/Table 4: The ulcerated tumor on the right parieto-occipital region with bone destruction.

Figure 29:



Patient 3/Table 4: Exophytic, ulcerated tumor mass on the back with suppurative inflammation and abscess formation.

Figure 30:



Patient 4/Table 4: Ulcerated tumor on the patient's presternal area.

Figure 31:



Patient 5/Table 4: BCC on the right side of the neck, two smaller squamous cell carcinomas on the preauricular region and on the ear.

6. Conclusions

6.1.1. Clonal nevi

The knowledge of the clinical and histopathological characteristics of clonal nevi is very important for the proper diagnosis of these nevi. As only 8 cases could be detected among 1267 nevi in 2006 this type of nevus can be considered as a very rare one. The diagnosis could be difficult however knowing the characteristic features it is straightforward. It prevents patients, clinicians and histopathologists from the consequences of the misdiagnosis of malignant melanoma.

6.1.2 Childhood melanoma

The diagnosis of melanoma in a child is difficult both for the clinician and the histopathologist. Very careful analysis of the histopathology material, consultation with experienced pathologists is always necessary in order to differentiate the lesion from other childhood melanocytic lesions such as Spitz's nevus or proliferative nodule. The precise diagnosis is crucial as the prognosis of childhood melanomas is favorable with proper treatment. In questionable cases the re-examination of the slides and long-term follow-up of the patient is needed. As these tumors are very rare the collection and analysis of sufficient data for prognostic purposes is very important though it takes decades. However these data are essential for improving treatment modalities.

6.1.3. Nevi and melanoma in tattoos

At present, the pathogenesis of melanoma developing in a tattoo is unknown. Mere coincidence cannot be ruled out however trauma, ultraviolet light, a photoallergic effect, or an inflammatory reaction may promote the malignant transformation. Clinicians and histopathologists should be familiar with the clinical and histological features if they are to make a correct diagnosis. Another important question is the management of melanocytic nevi localized in the tattoo area. To date the correlation of nevi and tattoos has not been studied. Dermatologists and histopathologists must be aware that the tattoo pigment can disguise changes in preexisting nevi. The subject is very important as tattooing came in fashion and it is to be expected that dermatologists will in the future have to deal with increasing numbers of melanocytic lesions in association with tattoos.

6.2.1. Merkel cell carcinoma

Feng et al. in 2008 isolated a previously unknown new human polyomavirus which they named Merkel cell polyomavirus (MCV) from MCCs. Accordingly they suggested that MCV has a role in the pathogenesis of MCC⁵⁸⁻⁶¹. There have subsequently been other reports⁶²⁻⁶⁴ of the same results and these observations prompted us to investigate the presence of MCV DNA sequences in Hungarian MCC patients. The presence of viral T antigen and/or viral capsid DNA sequences was demonstrated in 10 of the 12 MCC lesions. None of the comparative samples contained MCV DNA. Our results are very similar to those of Feng et al. and others⁵⁸⁻⁶¹ and our findings also strongly support the hypothesis that MCV infection may well be specific for MCC, and MCV may play a role in the pathogenesis of MCC.

6.2.2. Neglected basal cell carcinomas

Neglected advanced skin tumors can be encountered even in the 21st century. There can be numerous causes of the delay in the diagnosis: the person may fear the diagnosis and the treatment or become accustomed to the usually slowly-growing tumor. Old age, a low social milieu and an inadequate hygienic culture may also be factors explaining why some people are not aware of the significance of a delayed diagnosis.

BCC, the most common cutaneous tumor, usually develops in the elderly, grows slowly and has an extremely low metastatic potential making it an “ideal candidate” for a neglected tumor.

Although there are many possibilities for the treatment of BCCs, the therapy of such neglected, sometimes even mutilating cases always demands an individual and multidisciplinary approach and teamwork. However these custom-made operations and treatments are usually unable to eliminate the whole tumor mass, to hide or correct the mutilating destructions. The only way to avoid this situation should be prevention and even better health-care public education.

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