• M, 54 years
• left hand, exophytic growing neoplasm
• slowly enlarging neoplasm (5 years !)
• 9 x 9 cm, soft consistency
• biopsy
• complete excision
• no recurrence at 5 years
Diagnosis: spindle cell Lipoma?
Clinician: „You must be wrong with your diagnosis, do you want to see the patient?“
M, 62 years, left thigh, 9.1 cm
F, 60 years, back of hand, 3.5 cm, R at 6/12
Atypical Spindle Cell Lipomatous Tumor

Clinicopathologic Characterization of 232 Cases Demonstrating a Morphologic Spectrum

Aaron B. H. Rovner, MD, PhD, Alejandro L. Restrepo, MD, * James M. Fegen, MD, * Chien-Wen Liao, MD, and Christopher D.M. Fletcher, MD, * FRCPath

In this clinicopathologic review of atypical spindle cell lipomatous tumors, we present a series of histologic, immunohistochemical, and ancillary diagnostic features. The cohort included 232 cases of spindle cell lipomatous tumors, with a median age of 67 years (range, 22-87) and a male-to-female ratio of 5:1. The tumors exhibited a variety of histologic patterns, including wavy, elongated, and spindled cells, as well as a variable degree of cellular atypia. The tumors were classified as atypical (atypical spindle cell lipoma, atypical lipomatous tumor, and atypical lipomatous tumor with myxoid change) or malignant (atypical lipomatous tumor with dedifferentiated liposarcoma).

The median size of the tumors was 5 cm (range, 1-30 cm). The most common locations were the limbs (63%), limb girdles (63%), head/neck (10%), genital area (7%), trunk (6%), and back (6%). The tumors were poorly marginated and often infiltrated surrounding tissues.

Histologically, the tumors were characterized by a combination of lipomatous and spindle cell components. The lipomatous component was often myxoid, and the spindle cells showed variable cellular atypia. Immunohistochemically, the tumors were positive for CD34 and HHF-35, with variable expression of S100, SMA, and desmin.

Local recurrence was observed in 12% of cases (n = 27), with a median time to recurrence of 3 years. The tumors also demonstrated a high frequency of local recurrence, with 50% of cases showing local recurrence within 5 years of initial diagnosis. The overall survival rate was 80% at 5 years and 60% at 10 years, with a median follow-up of 2 years.

The classification of atypical spindle cell lipomatous tumors is challenging, as they can share features with both benign and malignant lipomatous tumors. The presence of atypical spindle cells and lipogenic cells is crucial in distinguishing these tumors from other spindle cell neoplasms. The management of these tumors is typically surgical, with the goal of achieving negative margins. However, the high rate of local recurrence highlights the need for careful follow-up and consideration of adjuvant therapy.

References


subcutis > deep soft tissues >> visceral admixture of atypical spindled + lipogenic cells
low cellularity (62%) > high cellularity (38%)
mild atypia (52%) > prominent atypia (28%)
uni- or multivacuolated lipoblasts (45%)
rare mitoses, no tumour necrosis
purely mroid to collagenous stroma
CD 34 + (64%), S-100 + (40%), desmin + (22%),
Rb loss (57%), no tumour MDM2 and CDK4 +
FISH analysis: no MDM2/CDK4 amplification
loss of Rb-1 locus in 71%
monosomy 7 in 43%
DD atypical spindle cell lipomatous Tumour

spindle cell lipoma: elderly male patients, neck, encapsulated, no atypia

ALT: $\text{MDM2} / \text{CDK4}$ amplification
no $Rb\text{-}1$ deletion

DDLS: deep soft tissue
abrupt transition, more atypia
$\text{MDM2} / \text{CDK4}$ amplification

spindle cell young patients, vasculature

myxoid LS: t(12;16), t(12;22)
(Alaggio R et al. AJSP 2009; 33: 645)

lipomatous SFT, diffuse neurofibroma, DFSP,
mammary-type myofibroblastoma, MPNST
Conclusions Case 12

ASCLTs are... distinct category of adipocytic neoplasms represent clinically low-grade neoplasms require surgical excision with clear margins low risk for local recurrence very low risk for dedifferentiation include „fibrosarcoma-like“ lipomatous neoplasms often adult males with predilection for the limbs variable proportions of atypical spindled cells, adipocytes, lipoblasts myxoid/coll. stroma CD 34 +, Rb -, MDM2 -, CDK4 -
Case 13: F, 3 months, back of left foot
Lipofibromatosis
Diagnosis Case 13

Lipofibromatosis
A clinicopathologic study of 45 pediatric soft tissue tumors with an admixture of adipose tissue and fibroblastic elements, and a proposal for classification as lipofibromatosis


32 M, 12 F, 1 ?, 8 tumours were present at birth, 1 - 7 cm distal extremities >> trunk/head
abundant adipose tissue + spindle shaped fibroblastic elements
limited cytologic atypia and proliferative activity
small collections of univacuolated cells (lipoblast-like cells)
focal expression of CD34, CD99, ASMA (desmin -)
regrowth/persistent disease in 17/22 patients (72%)
Chromosomal rearrangements in lipofibromatosis
5-year-old boy
three way t(4;9;6) translocation

Aberrant receptor tyrosine kinase signaling in lipofibromatosis:
a clincopathological and molecular genetic study in 20 cases
Al-Ibraheemi et al. Mod Pathol 2019; 32: 423-434
14 M, 6 F, 1 month-14 years
FN1::EGF in 4 cases (similar to calcifying aponeurotic fibroma)
activation of the PI3K/Akt/mTOR pathway
Case 14: M, 58 years, left upper arm
Diagnosis Case 14

cutanous PEComa
PEComa
(neoplasms with perivascular epithelioid cell differentiation)

- heterogenic family of neoplasms
- adult patients, F >> M
- angiomyolipoma, clear cell „sugar“ tumour,
  extrapulmonal clear cell „sugar“ tumour,
  lymphangioleiomyomatosis, uterine PEComa,
  PEComa of the skin and soft tissues
- broad anatomic distribution
- TSC aberrations in some neoplasms
- subset with TFE3 gene fusions (TFE3 +)
PEC - perivascular epithelioid cell

- „histogenesis“ ?, no nonneoplastic PECs
- epithelioid, spindled tumor cells
- clear, granular, pale eosinophilic cytoplasm
- round / oval, centrally localized nuclei
- network of thin-walled vessels
- perivascular growth
- expression of myogenic and melanocytic markers
- chromosomal aberrations (loss of 16p, 19, 17p, 1p, 18p, gains of X, 12q, 3q, 5, 2q)
PEComas – broad morphological spectrum
(Bonetti F et al. Adv Anat Pathol 1997; 4: 343)

round, cells cells spindled, eosinophilic cells

HMB45 expression

Aktin expression
Cutaneous PEComa*

- 15 F, 2 M, 15-81 years
- 15 x extremities (lower > upper), 2 x back
- dermal neoplasms, extension into subcutis
- network of capillaries, perivascular growth
- epithelioid > spindled tumour cells
- clear > granular, pale eosinophilic cytoplasm
- HMB45 +, MiTF1 +, NKIC3 +, Melan-A +/-, S-100 -, ASMA + (2), desmin +(6), CK -, h-caldesmon -, calponin –

Liegl B et al. AJSP 2008; 32: 608
Cutaneous PEComa does not harbour TFE3 gene fusions: immunohistochemical and molecular study of 17 cases

12 F, 5 M, median age: 49.5 years
clear cell / epithelioid or monomorphous clear cell pattern
TFE 3 -, SOX10 -
FISH-assay for TFE3 rearrangement was negative
DD: cutaneous PEComa

- clear cell dermatofibroma
- dermal clear cell neoplasm
  (AJDP 2004; 26: 273)
  large clear cells, vesicular nuclei
  NKIC3 +, melanocytic markers -
- clear cell AFX
- primary carcinoma / MTS of carcinoma
- clear cell sarcoma
DD: cutaneous PEComa

Clear cell dermatofibroma
(Zelger BW et al. AJSP 1996; 20: 483)

- epidermal hyperplasia
- rarely subcutaneous infiltration
- no network of capillaries
- no perivascular growth
- melanocytic markers -
DD: cutaneous PEComa

Clear cell atypical fibroxanthoma

- elderly patients
- face
- sun-damaged skin
- atypical cells
- many mitoses
- numerous mitoses
- melanocytic markers negative
M, 65 years, left groin
M, 67 years, left hip
History of renal cancer
M, 38 years, scalp
left calf, 9 cm mass 2 years before multiple MTS (lung, skin, nose....) metastasizing alveolar soft part sarcoma
PEComa with ASPSCR1::TFE3 fusion: expanding the molecular spectrum of TFE3-rearranged PEComa with an emphasis on overlap with alveolar soft part sarcoma
Zhao M et al. Histopathology 2024; 84: 482-491

2 F, 1 M, 21-51 years
rectum, kidney, cervix
epithelioid clear tumour cells
delicate vascular network
Melan-A +, ASMA +, TFE3 +
ASPSR1::TFE3 fusion
sclerosing PEComa
JL Hornick, CDM Fletcher AJSP 2008; 32: 493

- 13 patients, F, 34-73 years
- 1 patient with tuberous sclerosis
- retroperitoneum (10), pelvis, uterus, abdominal wall
- well-circumscribed neoplasms (11)
- tumour size 4.5 – 28 cm
- multiple MTS in one case
M, 76 Jahre, retroperitoneum
Melanotic PEComa: a rare but distinctive subtype analyzed in a series of 7 cases

21-82 years, pelvis (2), gallbladder, cervix, eyelid, epidural space, femur
heavily pigmented neoplasms
variably sized cells with granular > clear cytoplasm
HMB45 +, 6/7 TFE3 +, Melan-A -, S-100 -, desmin -, ASMA -
TFE3 rearrangement in 5/7 cases
SFPQ::TFEB in TFE3 negative case (patient died of disease)
Case 15: F, 34 years, paranasal region
epithelioid sarcoma
Diagnosis:

poorly differentiated squamous cell carcinoma in a young patient...
Diagnosis Case 15

epithelioid Sarcoma
EPITHELIAL SARCOMA

A Sarcoma Simulating a Granuloma or a Carcinoma

F. M. Ewing, MD

This article reviews the pathologic features and the behavior of 62 cases of a peculiar form of sarcoma that has repeatedly been confused with a chronic inflammatory process, a sequestrating granuloma, and a squamous cell carcinoma. The tumor occurs chiefly in young adults (median age 33 years) and may metastasize to the regional lymph nodes. It tends to grow in a nodular or multinodular manner along fascial planes and tendons, often with central necrosis of the tumor nodule and ulceration of the overlying skin. Most of the tumors grow slowly, and some had been present for months or years prior to surgery. Microscopically, the tumor consists of irregular nodular masses of large, deeply basophilic, polygonal cells containing a variable amount of hyaline collagen. Follow-up information on 18 patients (29%) revealed an overall clinical course with frequent recurrence (35%) and late metastasis (5%). Care may be achieved by wide local excision at early stage of disease.

The diagnosis of sarcoma, which is usually made only after biopsy, is based on the characteristic nodular arrangement and the epithelial appearance of the tumor cells. The characteristic nodular arrangement and the epithelial appearance of the tumor cells are usually seen early in the disease and the frequent involvement of the lymph nodes and facial structures were the principal features of the neoplasm that led to its early diagnosis. Initially we were under the impression that a tumor of this type had not been previously described, but a search of the literature revealed a similar case among reviews of epithelial sarcomas. In 1939, Berger described a "distinctive and peculiar" variant of epithelial sarcoma affecting the common extensor tendon of the right wrist. Although follow-up was incomplete, the tumor recurred rapidly after curative amputation and metastasized to regional lymph nodes.

From the Armed Forces Institute of Pathology, Washington, D.C.

Clinical records and microscopic sections of 62 cases of epithelial sarcoma described by Ewing, M., and Ewing, F.M., appeared in The American Journal of Pathology, 1939, 8(1), 1-9.

Figures 1A and 1B show a 24-year-old woman with a 10 cm diameter mass in the right knee, which was removed and labeled as a synovial sarcoma. The tumor had metastasized to the lungs and liver, and the patient died 2 years after diagnosis.

To cite this article: Ewing F.M., Ewing F.M. (1939). A Sarcoma Simulating a Granuloma or a Carcinoma. American Journal of Pathology, 8(1), 1-9.

The diagnosis of epithelial sarcoma is usually made only after biopsy, and the clinical course is characterized by slow growth and frequent recurrence. Metastasis to the regional lymph nodes is common, with late metastasis to the lungs and liver. A wide local excision is curative in early stage of disease, but in some patients, recurrence and late metastasis may occur.

INTRODUCTION

Since its first detailed description in 1939, epithelial sarcoma has been accepted as a unique soft tissue sarcoma which typically occurs in young adults. The tumor is usually slow-growing, and it may involve the skin, subcutaneous tissue, muscle, and bone. It may also spread to regional lymph nodes. Microscopically, epithelial sarcoma may resemble a variety of other soft tissue sarcomas, such as synovial sarcoma, malignant fibrous histiocytoma, and neurofibrosarcoma.

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W roku 1948 miałem możność klinicznego i histopatologicznego badania przypadku guza ręki, który przedstawiał poważne trudności diagnostyczne. Ostatecznie uświadomiłem sobie, że utkanie nowotworu jest nieznane i że jestem w stanie bliżej określić jego natury łkankowej. Z konieczności zatem ograniczającym się do ogólnoklinicznego rozpoznania siebie i próbókkowym rozpoznaniu bezlaskowego nowotworu oświetlającego. Preparat mikroskopowy powodziwał za granicę, gdzie jeden z profesorów, cieszący się wielkim autorytetem, rozpoznawał nietypową postać czerniaka. Z opinią tą nie mogłem się zgadzać; ani obrady kliniczne ani mikroskopowe nie przemawiały za czerniakiem. Wprost nawet przeciwieństwo - wskazywały na to, że nie jest to czerniak. Dalszy przebieg choroby i pomysłowy wynik leczenia potwierdziły moje stanowisko. Zgodnie z przyjętym w Zakładzie Patologii Instytutu Chorób Zakaźnych zaliczyłem przypadki do rzędu ząbkowatych i wyrażających gromadzenie dalszego materiału. W ciągu lat blisko 12 udało mi się zbadać tego rodzaju guzów. Dalej mogę z pewnością powiedzieć, że omawiane nowotwory ma swoje odrębne charakterystykę biologiczną i morfologiczną, wobec czego uzasadnionym jest jego wyodrębnienie jako oddzielnej i dotychczas nieznanej jednostki onkologicznej.


Proces nowotworowy rozwija się w tkankach łęknittych od strony powierzchni dłoniowej i jest, jak podają chorzy, chorych poprawa się bąba guz, lokalizowane są w twardym guzie, w tym miejscu guz w miejscu guza, w nacionalnej. Najczęściej nowotwór rozwija się w podwodnej lub w podwodnej. W jednym przypadku zmiana umiejscowiona była bliżej nadgarstka.

Wraz z guza odnosi się powolnie; stopniowo naciek od otochine. W tym również powikłania jągo skórę. Jak zaznaczymy - ma ona raczej wygląd bardzo twardego nacieka, stopniowo gubiącą się w otochine.

Józef Łaskowski
SARCOKA APONEUROTICUM
Z Zakładu Patologii Instytutu Onkologii
im. Marti Skłodowskiej-Curie w Warszawie
Dyrektor: prof. dr med. J. Łaskowski
Kierownik Zakładu Patologii: prof. dr med. J. Łaskowski

In 1948 I studied clinically and histopathologically a tumor of the hand which caused considerable diagnostic difficulties. Finally I became aware that the neoplastic tissue is unknown to me and that I am unable to determine its nature. Of necessity I confined myself to the vague diagnosis of a non-epithelial malignant neoplasm. The microscopic slide was made abroad where one of the professors of high authority recognized an atypical form of melanoma. I did not agree with this opinion: neither clinical data nor the morphologic pattern supported the diagnosis of a melanoma. On the contrary, it indicated that it is no melanoma. The further course of the disease and the favorable effect of therapy confirmed my opinion. According to the principle accepted in the Institute of Oncology we classified this case to the enigmatic ones and decided to collect further material. I succeeded in collecting seven cases of tumors of this type within almost 12 years. At present I can claim with certainty that this neoplasm

Józef Łaskowski
APONEUROTIC SARCOMA
Department of Pathology, Institute of Oncology in Warsaw

On the basis of histoclinical analysis of 7 cases recorded in the Institute of Oncology in Warsaw (Poland) in the period of 1949—1950 a new type of mesenchymal neoplasm originating from the aponeuroses and related structures has been distinguished. The tumor was situated almost exclusively on the palmar aspect of the hand just beneath the skin and appeared in the form of a flat, very hard infiltration. The growth was very slow and after some years a bluish-like deep ulceration with sharply outlined borders appeared in the skin of the palm, usually in the middle portion of the tumor. It was remarkable that this lesion affected mostly manual workers. Trauma seems to play an important role in the pathogenesis of the neoplasm. The patients recorded so far were aged 23—56 years. Microscopically, the neoplasm was composed of spindle cells intermingled with those of epitheloid appearance. The tumor shows a tendency to become fibrotic and to invade diffusely deep the adjacent tissues. Therefore contractures similar to those of Dupuytren sometimes do occur. The course of the disease is slow, lasting many years. The neoplasm is locally malignant, the borders are not sharply delineated and it is very prone to recur. In some cases the neoplasm metastasizes through the lymphatic or blood vessels. However, the results of treatment are encouraging if radical surgery is performed based on the knowledge of the biology of the tumor. Electrosection and electrocoagulation, removal of the lesion together with the corresponding fingers and metacarpal bones (possibly the formation of what is called "small hand") and at least amputation of the forearm can be taken into consideration. So far this neoplasm was falsely diagnosed as: malignant melanoma, malignant synovium, squamous carcinomatis, inflammatory process.
Epithelioid Sarcoma: A sarcoma simulating a granuloma or a carcinoma
F.M. Enzinger Cancer 1970; 26: 1029

- „acidophilic fascial Sarcoma“
- 62 cases, M > F
- x = 23 years
- hand, forearm, lower leg
- nodular / multinodular growth along tendons, neurovascular structures
- 85% R, 30% MTS, 20% DOD
M, 43 years, slowly growth within months
Histology / Immunohistochemistry

- nodular growth, central necrosis
- polygonal, epithelioid, spindled tumour cells
  slight atypia, scattered mitoses
- desmoplasia: fibroma-like variant
  pseudovascular clefts: angiomatoid variant
  calcification, ossifications, rare myxoid areas
- vimentin +, EMA +, pancytokeratin +, CD34 + (50%)
  CK 8 +, CK 14 +, CK 19 +
  ERG + (38%, Miettinen et al. AJSP 2013; 37: 1580-1585)
  CK 7 -, CK 20 -, CK 5/6 -, S-100 -, CD31 -
SMARCB1/INI1 tumor suppressor gene is frequently inactivated in epithelioid sarcomas

• long arm of chromosome 22
• suppressorgene, inhibition of proliferation
• induction of „cellular senescence“
• modulation of actin cytoskeleton
• inactivation in epithelioid sarcoma
• point mutation in renal / extrarenal malignand rhabdoid tumour
Infrequent *SMARCB1/INI1* gene alteration in ES


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epithelioid Sarcoma - Variants

1. Fibroma-like variant
   spindled > epithelioid cells, storiform growth
   DD: dermatofibromas, fibroma

2. Angiomatoid variant
   cystic, blood filled spaces
   DD: EHE, epithelioid angiosarcoma

3. Myxoid variant
   DD: Myxofibrosarcoma...

4. Proximal (large cells) variant
   nodular, sheeth-like growth
   large, rhabdoid tumour cells, necrosis
   DD: epith.AS, MTS-CA, rhabdoid Tumour
Spectrum of epithelioid Sarcoma

fibroma-like variant
angiomatoid variant
myxoid variant
proximal-type epithelioid Sarcoma

older age group than distal type
depth soft tissue, pelvis, perineum, intracavitary
represents morphological form of progression
aggressive clinical course
inactivation of INI1/SMARCB1 (ch 22q11)
IM: positive: vimentin, EMA, cytokeratin
CD34 (50%)
desmin rarely
ERG (10-60%)
negative: INI1
CD31
F, 57, chest wall
sheets of large, epithelioid tumour cells
enlarged epithelioid and rhabdoid tumour cells
proximal-type myxoid variant
M, 11 years, right thumb
proximal type epithelioid sarcoma in distal location
Relationship of epithelioid sarcoma and proximal-type epithelioid sarcoma

Proximal-type epithelioid sarcoma represents the morphological form of progression of epithelioid sarcoma....
Molecular profiling and immunohistochemical characterization unveils differences between classic-type and proximal-type epithelioid sarcoma
(F Cappello et al. USCAP 2023)

11 classic-type epithelioid sarcoma
8 proximal-type epithelioid sarcoma

classic-type ES: expression of genes involved in cell adhesion and migration
GATA3 -, CDH2/N-Cadherin 4/6 +

proximal-type ES: expression of genes involved in chromatin remodeling and cell cycle regulation
GATA 3 5/8 +, CDH2/N-Cadherin -
„Classic-type and proximal-type epithelioid sarcoma represent two biologically distinct entities based on their different transcriptional profiles!“
DD: proximal-type epithelioid Sarcoma

epithelioid haemangioendothelioma:
  no solid growth, CD31 +
epithelioid angiosarcoma:
  cytoplasmic vacuoles, erythrocytes, CD31 +
epithelioid MPNST (INI1 loss in 50%):
  mixed growth (nests, cords), S-100 +
malignant rhabdoid tumour:
  infants, CD 34 -
myoepithelial tumours (may show INI1 loss):
  myxoid stroma, duct formation, more heterogenous, EWSR1 rearrangement
Case 16: F, 44 years, right hand, 4th finger
FISH-Analysis:

*STAT6-GLI1-DDIT3- HMGA2-CDK4-MDM2* amplification

(Prof.Antonescu CR, New York)
Diagnosis Case 16

GLI1-amplified soft tissue neoplasm
GLI1-altered epithelioid soft tissue neoplasms

A distinct malignant epithelioid neoplasm with GLI1 gene rearrangements, frequent S100 protein expression and metastatic potential: expanding the spectrum of soft tissue neoplasms defined by GLI1 gene fusions

Antonescu CR et al. AJSP 2018; 42: 553-560

6 cases, 4 F, 2 M, 16-79 years
lower extremities, retroperitoneum, trunk, head/neck lymph node metastases (3), lung metastases (1)
monomorphic epithelioid phenotype
nest or cord-like architecture, capillary network
S-100 + (4/6); GLI1 fusions with ACTB, PTCH1, MALAT1
GLI1 amplifications expand the spectrum of soft tissue neoplasms defined by GLI1 gene fusions
Agaram NP et al. Mod Pathol 2019; 32: 1617-1626

10 cases, 5 F, 5 M, 4-65 years
limbs, trunk, head and neck
growth pattern
epithelioid tumour cells, nested growth pattern
increased nuclear pleomorphism, many mitoses
necrosis, lymphovascular invasion

GLI1 amplification, coamplification of MDM2, CDK4, STAT6

GLI1 amplification represents an alternative genetic mechanism of GLI1 oncogenic activation
Head and neck mesenchymal neoplasms with GLI1 gene alterations. A pathologic entity with distinct histologic features and potential for distant metastasis

11 cases (8 x tongue, 1-65 years)
multinodular growth, delicate vascular network
momtonous round to ovoid nuclei, pale/clear cytoplasm
GLI1 fusions (7 x), coamplification GLI1/MDM2/CDK4 (4 x)
S100 +, CD56 +, CDK4/MDM2/STAT6 + in amplified cases
distant metastases in 2 out of 6 patients with follow-up
Distinctive nested glomoid neoplasm. Clinicopathologic analysis of 20 cases of a mesenchymal neoplasm with frequent GLI1 alterations and indolent behavior

20 cases, (11 F, 9 M), congenital to 74 years, 0.9 - 11.1 cm trunk (7), lower (5) and upper limbs (3), tongue (4), neck (1) nests of round to ovoid tumour cells network of capillaries, perivascular growth microcysts (8), myxoid stroma (5), clear cells (7) MDM2 + (47%), S100 + (26%), STAT6 + (20%), CK (10%) GLI1 alterations (16) GLI1 rearrangements (10) GLI1 amplifications (6) local recurrences (30%), no MTS, no DOD
Case 17: M, 83 years, neck
Diagnosis Case 17

dedifferentiated Liposarcoma with distinctive nested glomoid neoplasm-like features
Case 18: F, 72 years, right hand
Sox10

Melan-A
Diagnosis:

Clear cell sarcoma...

But

RT-PCR: no *EWS* or *ATF1* translocation
CRTCI-TRIM 11 RT-PCR

Marker  21 K 000403  Negativkontrolle

200 bp  | Referenzbande chimäres CRTCI-TRIM 11 RT-PCR-Produkt
150 bp  |
Diagnosis Case 18

Cutaneous melanocytoma with CRTC1::TRIM11 fusion
Cutaneous melanocytoma with \textit{CRTC1-TRIM11} fusion

recently described, rare neoplasm
children, adults
wide variety of anatomic locations
low-grade neoplasms (R and MTS are rare)
Differential diagnosis:
  cellular blue naevus
  metastatic and dermal melanoma
  paraganglioma-like dermal melanocytic TU
  clear cell sarcoma
Cutaneous melanocytoma with *CRTC1-TRIM11* Fusion: Report of 5 cases resembling clear cell sarcoma

Cellier L et al. AJSP 2018; 42: 382-391

3 F, 2 M, 25-82 ys, extremities (3), trunk (1), neck (1) nodular, dermal neoplasms, nests and bundles of spindled, epithelioid tumour cells, multinucleated giant cells, cytological atypia, mitoses, necrosis (2) positive staining of melanocytic markers *CRTC1-TRIM11* fusion, nuclear TRIM11 + no *EWS* translocation no local recurrence, no metastasis (3-72/12)
"CRTC1-TRIM11 fusion defined melanocytic tumors: A series of four cases (Ko JS et al. J Cutan Pathol 2019; 46: 810-818)

A case report of cutaneous melanocytoma with "CRTC1-TRIM11" fusion: is CMCT different from clear cell sarcoma of soft tissue? (Kashima J et al. Pathol Int 2019; 69: 496-501)

Dermal melanocytic tumor with "CRTC1-TRIM11" fusion: report of two additional cases with review of the literature of an emerging entity (Parra O et al. J Cutan Pathol 2021; 48: 915-924)

Cutaneous melanocytic tumor with "CRTC1::TRIM11" fusion and prominent epidermal involvement Vest BE et al. J Cutan Pathol 2022; 49: 1025-1030
Cutaneous melanocytoma with \textit{CRTC1::TRIM11} Fusion: An emerging entity analyzed in a series of 41 cases

23 F, 18 M, 11-87 years (mean age: 44 years) 
limbs (36), trunk (8), mucosa (2), head (1), ? (4) 
dermis, sometimes exophytic growth, nodular lesions intersecting nests and bundles 
low mitotic activity (< 5 mitoses/10 hpf), necrosis (2) 
Sox10 +, S-100 focally +, Melan-A focally +, TRIM1 + 
\textit{CRTC1-TRIM11} fusion 
20/22 cases free of disease (12-168 months FU) 
1 local recurrence at 6/12 
1 multiple nodal metastases at 13/12
DD: Cutaneous melanocytoma with *CRTC1::TRIM11* fusion: cellular nevus blue
DD: Cutaneous melanocytoma with *CRTC1::TRIM11* fusion: metastatic and primary dermal melanoma

intersecting nests and bundles

uniformity of the cytology

*CRTC1::TRIM11* fusion
F, 44 years, trunk
Diagnosis: dermal melanoma
DD: Cutaneous melanocytoma with \textit{CRTC1::TRIM11} fusion: Paraganglioma-like dermal melanocytic tumor


6 F, 2 M, 18-53 years
nodular, multinodular (3)
mild atypia, low proliferative activity
similar immunophenotype
intact EWS locus
But: no testing of \textit{CRTC1-TRIM11} fusion
nests and fascicles of spindled cells
„wreath-like giant cells“
FISH Analysis for the evidence of *EWS* translocation with a *EWS*-break apart probe
inguinal lymph node metastasis
Diagnosis:
dermal clear cell sarcoma
M, 42 years
Cutaneous Clear Cell Sarcoma: A Clinicopathologic, Immunohistochemical, and Molecular Analysis of 12 Cases Emphasizing its Distinction from Dermal Melanoma

Markus Hantschke, MD,* Thomas Mentzel, MD* Arno Rütten, MD* Gabriele Palmada, PhD* Eduardo Calonje, MD† Alexander J. Lazar, MD† and Heinz Kutzner, MD*

Abstract: Clear cell sarcoma (CCS) of tendons and aponeuroses/ malignant melanoma (MM) of soft parts is a rare tumor and in the majority of cases presents a characteristic reciprocal translocation t(12;22)(q13;q12) that results in fusion of the EWS and ATP7 genes. Although the melanocytic differentiation of CCS is indistinguishable, its precise lineage remains unclear. Typically, the slowly growing tumor affects the extremities of adolescents or young adults, especially around the ankle and foot. CCS is classically regarded as a deep soft tissue tumor associated with tendons or aponeuroses. This traditional view is put into perspective by the description of primary CCS of the gastrointestinal tract that may have a variant fusion gene EWSR1-CREBBP. We describe 12 cases of cutaneous CCS and discuss the differential diagnoses. These 12 cases share an identical immunohistochemical profile with MM and thus can easily be confused with a dermal variant of spindle cell MM of metastasis of MM. The patient’s ages ranged from 6 to 74 years (median: 25 years), and there were 6 females and 6 males. Most tumors (n = 9) were located on the extremities, 2 tumors arose on the back, and 1 on the abdomen. The mean tumor size was 6.9 cm (range, 4.0 to 17 cm). Six cases showed invasion of the subcutis, the other 6 cases were entirely dermal. Tumor necrosis was evident in 2 cases, melanoma pigment in 2 cases, and ulceration in 1 tumor. All cases showed uniform nests and fascicles of spindled or slightly epithelioid cells with fine granular eosinophilic or clear cytoplasm. There was no nuclear pleomorphism with plump spindled nuclei and significantly prominent nucleoli. Multinucleated tumor giant cells were observed in two-thirds of cases, but were usually present only focally. The dermal collagen aggregates were crowded by delicate fibrous septa. The stroma showed a sclerotic, reticulated pattern. Partial, the nests of spindle cells bordered the epidermis, prongs reaching branched nests of melanocytes. The specific translocation pattern was confirmed in all cases by fluorescence in situ hybridization. Local recurrences and metastases developed in 2 and 3 patients, respectively, and 1 patient died of the disease.

Key Words: clear cell sarcoma; melanoma of soft parts; melanoma

(Ann J Surg Pathol 2010;34:216-222)

Clear cell sarcoma (CCS) of tendons and aponeuroses/ malignant melanoma (MM) of soft parts is a unique sarcoma initially described by Franz Enzinger in 1965.10 The tumor has a proclivity to involve the tendons and aponeuroses of distal extremities of adolescents or young adults, with a peak incidence in the third and fourth decade and a slight female predominance. The tumor is usually deep seated and characterised by multiple local recurrences with late metastases and a high rate of tumor deaths. Pathologic findings include fascicles and nests of pale fusiform and epithelioid tumor cells with finely granular eosinophilic or clear cytoplasm. There was no nuclear pleomorphism with plump spindled nuclei and significantly prominent nucleoli. Multinucleated tumor giant cells were observed in two-thirds of cases, but were usually present only focally. The dermal collagen aggregates were crowded by delicate fibrous septa. The stroma showed a sclerotic, reticulated pattern. Partially, the nests of spindle cells bordered the epidermis, prongs reaching branched nests of melanocytes. The specific translocation pattern was confirmed in all cases by fluorescence in situ hybridization. Local recurrences and metastases developed in 2 and 3 patients, respectively, and 1 patient died of the disease.
Compound clear cell sarcoma of the skin -
A potential diagnostic pitfall:
Report of a series of 4 new cases and
a review of the literature

- M, 17-71 years, lower extremities (2), head (1), trunk (1), 8 - 55 mm
- 3 primary tumour, 1 skin metastasis
- typical features in the dermis + intraepidermal component (nests of spindled and epithelioid tumour cells)
- *EWSR1* rearrangement in all 4 cases
RT-PCR for fusion of EWS Exon 7-ATF1 Exon 5 with beta-Actin as control of amplification

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1=EWS Exon 8/ATF1 Exon 4
2=EWS Exon 7/ATF1 Exon 5
3=EWS Exon 9/ATF1 Exon 7
4=EWS Exon 7/CREB1 Exon 7

Referenzbereich chimäres EWS-ATF und EWS-CREB1 RT-PCR-Produkt
Cutaneous melanocytoma with \textit{CRTC1::TRIM11} Fusion: An emerging entity analyzed in a series of 41 cases

„CCS represents the entity morphologically closest to cutaneous melanocytoma with \textit{CRTC1-TRIM11} fusion“

„deeper anatomic location, multinucleated giant cells and, in some cases, prominent clear cell morphology in CCS“

„molecular confirmation will still be needed“
MITF pathway-activated melanocytic tumours

Clear cell tumor with melanocytic differentiation and 
*MITF-CREM* translocation: a novel entity similar to 
clear cell sarcoma  
(de la Fouchardiere A et al. Virchows Archiv 2021; 479: 841)

Clear cell tumor with melanocytic differentiation and 
*ACTIN-MITF* translocation: report of 7 cases of a 
novel entity  

*MED15*:ATF1-rearranged tumor: a novel cutaneous tumor 
with melanocytic differentiation  
(Ko JS et al. Mod Pathol 2024; online ahead of print)  
5-16 years, high proliferative activity  
Case 3: lymph node metastases
What defines a neoplasm?

- Characteristic clinical features?
- Characteristic morphology?
- Typical immunophenotype?
- Characteristic molecular features?
- Characteristic methylation pattern?
Cutaneous melanocytoma with *CRTC1::TRIM11* Fusion

unique nosologic entity?

CCS with *CRTC1::TRIM11* fusion?
(and better prognosis)

???
Case 19: M, 67 years, right shoulder
sarcomatoid MM
sarcomatoid MM
sarcomatoid MM
sarcomatoid MM
Diagnosis Case 19:

undifferentiated pleomorphic sarcoma (superficial „MFH“)
Diagnosis Case 19

sarcomatoid malignant Melanoma
Metastatic malignant melanoma with complete loss of differentiation markers (undifferentiated/dedifferentiated melanoma): analysis of 14 patients emphasizing phenotypic plasticity and the value of molecular testing as surrogate diagnostic marker


undifferentiated/spindle cell sarcoma morphology
S-100 -, Melan-A -, HMB-45 -, Sox10 -
BRAF mutation (5), NRAS mutation (5)

Prame expression is a useful tool in the diagnosis of primary and metastatic dedifferentiated and undifferentiated melanoma


11 primary and 10 metastatic cases: strong nuclear PRAME expression AFX and PDS PRAME -, weak and patchy +
Case 20: M, 48 years, left knee
OFMT without bone
OFMT without bone
CD 31 -, ASMA -, Calponin -, CK -, HPCA1 -, EMA -, MUC4 -, desmin -
by courtesy of Prof. Dr. A. Agaimy, Erlangen, Germany
Diagnosis Case 20

ossifying fibromyxoid Tumour
(without bone)
Ossifying fibromyxoid Tumour

Adult patients, subcutis > deep soft tissue, extremities > head, trunk

MRI: well-circumscribed, lobulated, peripheral calcification/ossification

Uniform round to spindled tumour cells, cords, nests, sheets

Variable cellularity, low mitotic activity

Fibrous and myxoid stroma

Fibrous septa, capsule, pseudocapsule

Peripheral shell of metaplastic bone

S-100 + (65%), desmin + (50%), EMA +/-, CK +/-, ASMA +/-

INI1 - in 75%

Most commonly PHF1 fusions
Case 21: M, 54 years, abdominal wall
kappa light chain

lambda light chain
Patient is suffering from Diabetes Type 1 since many years...
Insulin injection since years
Diagnosis Case 21

nodular amyloidosis at the site of insulin injection
Nodular amyloidosis at the sites of insulin injections

2 diabetic patients
longstanding subcutaneous insulin treatment
subcutaneous nodules at the sites of injection
eosinophilic and amorphous masses
Congored +, amyloid P-substance +, insulin antibody
Amyloid is characterized by fibrillar ultrastructure
> 20 proteins are possible precursors
„The amyloidoses are a group of protein misfolding
diseases characterized by the accumulation in extracellular
spaces of insoluble fibrillar protein“
Case 22: M, 56 years, supraclavicular area
Pancytokeratin (MNF116)
EM Findings: tonofilaments, desmosomes
Diagnosis Case 22

Branchioma
(ectopic hamartomatous Thymoma)
Branchioma

- Smith PC, McClure J J Clin Pathol 1982; 35: 1074
  unusual subcutaneous mixed tumour exhibiting adipose, fibroblastic
  and epithelial components
- Rosai J et al. AJSP 1984; 8: 501
  „ectopic hamartomatous thymoma“ - thymic origin?
- Fetsch JF, Weiss SW Hum Pathol 1990; 21: 662
  arises from the 3rd/4th pharyngeal pouch, cervical sinus
- Chan JKC, Rosai J Hum Pathol 1991; 22: 349
  thymic or related branchial pouch differentiation
- Michal M et al. Histopathology 1996; 29: 549
  heterotopic salivary differentiation is suggested
- Fetsch JF et al. AJSP 2004; 28: 1360
  no true evidence of thymic differentiation, branchial anlage mixed tumour
Branchioma
Pathological Findings

- well-circumscribed lesions, 1.5 – 19 cm
- fibroblast-like, bland spindled cells showing myoepithelial phenotype (AJSP 2004; 28: 1360)
- epithelial structures (tubules, glands, squamous areas, cysts, trabecular network)
- mature adipocytes, scattered lymphocytes
- rarely myoid/clear cell differentiation
- very rarely carcinomatous features
- vimentin +, CK +, CD34 + stromal cells
branchioma
M, 51 years, jugulum
Carcinoma arising in ectopic hamartomatous thymoma

(Michal M et al. Zentralbl Pathol 1993; 139: 381-386)
Branchioma: immunohistochemical and molecular genetic study of 23 cases highlighting frequent loss of retinoblastoma 1 immunoexpression
Bradova M et al. Virchows Archiv 2024; 484: 103-117

21 M, 2 F, 31-80 years, 10-80 mm, simple excision, no R, no MTS supraclavicular (11), suprasternal (8), chest wall (2), neck (1), back (1) admixture of spindle cells, epithelial cells, adipose tissue neuroendocrine morphology (1), myoid differentiation (1) multinucleated giant cells (1), prominent clear cells (1) carcinoma in the background of branchioma (3) AE1/3 +, p63 + (spindled + epithelial cells) CD34 + (spindled cells), Rb1 - (13/15 cases)
Case 1:  *MSH6, PETEN, KRAS* mutations
Case 2:  *BMPR1A, TET2* mutations
Case 14:  *BRCA1* mutation
Case 20:  *FANCG* mutation
Case 21:  variants of unknown significance (*PHOX2B, XRCC2, PLCG2*)
Case 22:  *NF2, NF1* mutations
Case 19:  *HRAS, PIK3CA, CHD2, SLIT2* mutations
(CA ex branchioma)
C. 14,18:  deletion of *RB1*
DD: Branchioma

- poorly differentiated squamous cell carcinoma (mitoses, necrosis)
- MPNST (MPNST with glands)
- biphasic synovial sarcoma
- mixed tumour of the skin
- thymolipoma
- ectopic cervical thymoma
- SETTLE
- CASTLE
Spindle epithelial tumour with thymus-like differentiation (SETTLE)

- children, young adults, thyroid nodule
- spindled cells, epithelial cells
- sclerotic bands, reticular pattern
- homogenous cytokeratin expression
- rare monophasic spindle cell differentiation
- rare myoepithelial differentiation
- documented Ki-ras gene mutation
- no convincing proof of thymic differentiation
- 5/15 MTS, 3/15 DOD
Spindle epithelial tumour with thymus-like differentiation (SETTLE)*

* by courtesy of Prof.J.K.C Chan, Hong Kong
Carcinoma showing thymus-like differentiation (CASTLE)

- adult patients, thyroid or neck mass
- lobular pattern, fibrous septa
- atypical cells with indistinct borders, vesicular nuclei and prominent nucleoli
- focal squamous differentiation
- lymphocytes, plasma cells
- CK +, thyroglobulin -, calcitonin -
- increased risk for R and MTS
Carcinoma showing thymus-like differentiation (CASTLE)*

* by courtesy of Prof.J.K.C Chan, Hong Kong
Case 23:
M, 82 years
left lower leg
previous TEP knee
Podoplanin (D2-40)
CD20 -, CD2 -, CD30 -
Diagnosis Case 23: intralymphatic Histiocytosis
(Requena L et al. AJDP 2009; 31: 140-151)

• 16 cases, F > M, upper > lower extremities
• dermal lesions (stratum retikulare)
• ill-defined, erythematous plaques
• dilated lymphatic vascular spaces (podoplanin + endothelial cells)
• intravascular histiocytes
  (CD 68 +, CD 14 +, CD 31 +)
• associated inflammatory infiltrate
• associated rheumatism in 50% of cases!
• relationship with metal implant (Int J Dermatol 2014; 53: e365)
• indolent but chronic course
by courtesy of Dr. L. Requena, Madrid, Spain
Many thanks for your attention…