Dermatopathology: Update in cutaneous soft tissue tumours

Update in cutaneous soft tissue tumours in children

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Connective tissue nevi:
- collagen type (collagenoma)
- elastin type (elastoma)
- collagen and elastin type (mixed)
- cellular (fibroblastic) type

Connective tissue nevi: An entity revisited

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Background: Connective tissue nevi (CTN) may be isolated, either sporadic or hereditary, or syndromic as in the Buschke-OLofsondoff syndrome. Few publications have addressed the variable clinical and histopathologic expression of these benign hamartomas.

Objective: We sought to characterize the clinical and histopathologic features of CTN and to highlight a spectrum of clinical disease.

Methods: We carried out a retrospective study of cases selected after strict clinical and histopathologic confirmation of the diagnosis.

Results: A total of 33 patients with CTN were included. The average age of onset was 2 years. Three clinical forms were distinguished: type A with lesions at a single site, with one case presenting as an ulcerated infiltrated plaque; type B with two or more sites of involvement, and type C with unusually severe infiltration with functional impairment of a limb. Histopathologic examination of lesional biopsy specimens showed 10 collagenomas, one elastoma, 18 mixed CTN, and an increased number of fibroblasts in 4 cases. No correlation between clinical type and histopathologic findings was observed.

Limitation: This was a descriptive case series.

Conclusions: CTN comprise a clinical spectrum ranging from isolated papules to unusually severe aggressive plaques with monomorphic involvement. The histopathologic features are heterogeneous and include a newly described variant, which we name “cellular CTN” because of the increased number of fibroblasts. (J Am Acad Dermatol 2012;67:233-9.)
Collagen type (collagenoma)

Elastin type (elastoma)

Fibroblastic type
Series of 25 cases. 16 F, 9 M

Age at presentation ranging from 1.5 to 58 years (median 10 y)

Size ranged from 0.3 to 2 cm

Solitary slowly growing, painless, plaque or nodule

Trunk>head and neck>>limbs

Mainly situated in the reticular dermis and superficial subcutis

Proliferation of bland fibroblastic/myofibroblastic cells arranged in short intersecting fascicles

No significant cytologic atypia

Fibroblastic Connective Tissue Nevus

A Rare Cutaneous Lesion Analyzed in a Series of 25 Cases

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Abstract: Fibroblastic connective tissue nevus (FCTN) represents a rare and distinct benign cutaneous mesenchymal lesion of fibroblastic/myofibroblastic lineage, which broadens the spectrum of lesions presently recognized as connective tissue nevi. A series of 25 cases of FCTN has been analyzed to further characterize the clinicopathologic spectrum and immunohistochemical features of this entity. Sixteen patients were female (64%) and 9 were male (36%), with age at presentation ranging from 1.5 months to 58 years (median, 10 y). Most patients presented with a solitary, slowly growing, painless plaque-like or nodular skin lesion. Eleven cases (44%) arose on the trunk, 9 (36%) on the head and neck, and 5 (20%) on the limbs. The lesion was present for a median duration of 11.5 months (mean, 13.2 mo). Grossly, the lesions were tan-brown to tan-white, smooth, and firm. Their size ranged from 0.3 to 2.6 cm in greatest dimension (mean size, 0.67 cm; median, 0.6 cm). All tumors showed poor circumscription and were situated primarily in the reticular dermis, extending into the superficial subcutis in 13 cases (52%). The lesion was associated with papillomatous epidermis in 17 cases (70%) and the presence of adipose tissue in the reticular dermis in 14 cases (60%). All tumors were composed of a proliferation of bland intradermal fibroblastic/myofibroblastic cells with indistinct pale eosinophilic cytoplasm and tapering nuclei, with no significant cytologic atypia or pleomorphism, arranged in short-intersecting fascicles and entrapping appendages. No mitoses were identified. Immunostains showed positivity for CD34 in 20 of 22 cases (87%) and weak focal positivity for smooth muscle actin in 9 of 19 cases (47%). No case stained positively for desmin or S-100 protein. Clinical follow-up was obtained for 14 patients (median duration, 4 y). No tumor recurred locally, even when surgical excision was incomplete. No lesion metastasized. FCTN occurs most commonly as a plaque on the trunk and head/neck of children, involves deep dermis and superficial subcutis, and stains mainly for CD34. FCTN most likely represents a localized developmental dermal anomaly; it is entirely benign and should not be confused with dermatofibrosarcoma protuberans or other neoplasms such as dermatomyofibroma.

Key Words: fibroblastic connective tissue nevus, tumor, soft tissue, skin


An increasing number of dermal mesenchymal neoplasms showing a fibroblastic/myofibroblastic line of differentiation have been reported in the past decades, such as dermatofibroma,1 dermatofibrosarcoma protuberans (DFSP),2–4 atypical fibroxanthoma,5,7 pleomorphic fibrohistiocytic tumor (PFHT), solitary cutaneous myofibroma,6 and intradermal nodular fasciitis.8 Because some of these entities exhibit different clinical behavior, it is important to distinguish them histologically and to classify them accurately to avoid inappropriate treatment. The classification of these entities rests mainly on their distinctive and reproducible histologic features, their clinical context, and sometimes their immunophenotype.

Dermal mesenchymal tumors showing CD34 expression comprise a heterogeneous group of fibroblastic tumors such as “plaque-like CD34-positive dermal fibroma” (medial-like dermal dendrocyte hamartoma),9 DFSP,10,11 nuchal fibroma,12 solitary fibrous tumor,13 desmoplastic fibroblastoma/collagenous fibroma,14 spindle cell lipoma,15,16 and subsets of connective tissue nevi (CTN).14,15 CTN are rare benign hamartomatous lesions characterized histologically as discrete areas within the papillary or reticular dermis, where a clear predominance or depletion of collagen, elastin, or glycosaminoglycans may be found.15,16 Lesions in which collagen predominates are called collagenomas15,16; lesions in which elastic predominates are called elastomas.15,16 CTN may be solitary or multiple, sporadic or inherited, and may be associated with a number of syndromes (e.g. familial cutaneous collagenomas associated with cardiac disease,20 multiple collagenomas associated with MEN 121,22 stellate collagenomas associated with Cowden disease,17 Sharpey’s patches in tuberous sclerosis,22 and plantar cebreform collagenomas associated with protein S 23,24). With the notable exception of CTN associated with inherited syndromes in which a causal mutation is identified,22,23 the etiology of most CTN remains largely unknown. Lesions within the clinicopathologic spectrum of CTN but with more cellular fibroblastic morphology have not formally been described.
CD34 + 87%, SMA + (weak and focal) 47%

Should not be confused with:

- dermatofibrosarcoma protuberans $\rightarrow$ FISH
- dermatomyofibroma
- plexiform fibrohistiocytic tumor, fibroblastic type
Pseudo-tumoral forms of fibroblastic connective tissue nevi

Novel KHDRBS1-NTRK3 rearrangement in a congenital pediatric CD34-positive skin tumor: a case report

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Abstract

Cutaneous spindle-cell neoplasms in adults as well as children represent a frequent dilemma for pathologists. Along this neoplasm spectrum, the differential diagnosis with CD34-positive proliferations can be challenging, particularly concerning neoplasms of fibrohistiocytic and fibroblastic lineages. In children, cutaneous and superficial soft-tissue neoplasms with CD34-positive spindle cells are associated with benign to intermediate malignancy potential and include lipofibromatosis, plaque-like CD34-positive dermal fibroma, fibroblastic connective tissue nevus, and congenital dermatofibrosarcoma protuberans. Molecular biology has been valuable in showing dermatofibrosarcoma protuberans and infantile fibrosarcoma that are characterized by COL1A1-PDGFB and ETV6-NTRK3 rearrangements respectively. We report a case of congenital CD34-positive dermohypodermal spindle-cell neoplasm occurring in a female infant and harboring a novel KHDRBS1-NTRK3 fusion. This tumor could belong to a new subgroup of pediatric cutaneous spindle-cell neoplasms, be an atypical presentation of a plaque-like CD34-positive dermal fibroma, of a fibroblastic connective tissue nevus, or represent a dermatofibrosarcoma protuberans with an alternative gene rearrangement.
Overlaps
Medallion-like dermal dendrocyte hamartoma: the main diagnostic pitfall is congenital atrophic dermatofibrosarcoma

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Summary

Medallion-like dermal dendrocyte hamartoma is a newly described and rare clinical and pathological entity. This congenital, round, oedematous and atrophic lesion in the dermis is histologically characterized by a CD34+ dermal and hypodermal spindle-cell infiltration. We describe the clinical, histopathological, cytological and molecular features of three cases of dermal dendrocyte hamartoma. In all of the cases, atrophic congenital dermatofibrosarcoma procutaneum (DFSP) was the first histological diagnosis. In one case, wide surgery had been performed on the basis of the clinical and histological presentation. The histological pattern was similar to the all cases epidermal atrophy and a spindle to oval cell proliferation in the dermis and the subcutaneous fat. Immunohistochemical staining for CD34 and factor XIIIa was positive. Cytogenetic and molecular studies were performed, no chromosomal abnormality nor translocation (t(17;22)(q12;q14)) was observed. Fluorescence in situ hybridization analysis did not reveal the DFSP fusion gene COL1A1-PDGFB. We observed that the main diagnostic pitfall of medallion-like dermal dendrocyte hamartoma is atrophic congenital DFSP due to clinical and histological similarities. We emphasize that molecular studies to confirm the t(17;22)(q12;q14) translocation of DFSP may provide diagnostic elements for diagnosis in order to avoid unnecessary mutilating surgery.
Plaque-like CD34 positive dermal fibroma (Kützner)

Plaque-like CD34-positive Dermal Fibroma
(“Medallion-like Dermal Dendrocyte Hamartoma”)

Clinicopathologic, Immunohistochemical, and Molecular Analysis of 5 Cases Emphasizing Its Distinction From Superficial, Plaque-like Dermatofibrosarcoma Protuberosans

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Abstract: Medallion-like dermal dendrocyte hamartoma (DH) and superficial (plaque-like) dermatofibrosarcoma protuberosans (DFSP) are CD34-positive dermal neoplasms with overlapping clinicopathologic features. We analyzed the clinical, histomorphologic, and molecular criteria of 5 DH and 7 DFSP to delineate diagnostically relevant differences between incipient DFSP and the benign look-alike DH. We expand the clinical and histologic spectrum of DH. As medallion-like dermal DH is neither of dermal dendrocytic lineage nor a genuine hamartoma, we propose instead the descriptive term plaque-like CD34-positive dermal fibroma (PDF). Both PDF/DH and DFSP present as slightly pigmented and indurated plaques on neck, trunk, and extremities. Histologically, DFSP was characterized either by horizontally oriented spindle cell fascicles or by diffusely arranged fibroblasts within a slightly myxoid stroma in the upper two-thirds of the dermis, whereas PDF/DH presented with a cellular band-like fibroblastic proliferation mostly in the papillary and adjacent upper reticular dermis. Only one congenital PDF/DH in a 9-year-old boy extended into the septa of the subcutaneous fat. Formalin-fixed paraffin-embedded archival tissue was used for detection of the COL1A1-PDGFB gene rearrangement by multiple reverse transcription-polymerase chain reaction (RT-PCR) and by dual color fluorescence in-situ hybridization (FISH). Archival blocks older than 4 years did not yield amplifiable RNA because of RNA degradation, whereas FISH analysis was feasible in all investigated cases. FISH analysis revealed COL1A1-PDGFB gene rearrangement in all DFSP cases (n = 7), whereas RT-PCR could detect the COL1A1-PDGFB fusion transcript only in 1 DFSP. Two cases were negative. In 4 archival cases with storage between 4.5 and 17 years, RNA had been degraded making these cases unsuitable for RT-PCR. In PDF/DH, both RT-PCR and FISH analysis did not reveal any evidence of COL1A1-PDGFB gene rearrangement. We show that PDF/DH and superficial (plaque-like) DFSP, while clinicopathologic differences notwithstanding, are morphologic look-alikes that can be kept apart by molecular studies of the COL1A1-PDGFB gene fusion. For the detection of the COL1A1-PDGFB gene rearrangement in diagnostically difficult cases, RT-PCR and FISH analysis are reliable and helpful diagnostic tools. In archival formalin-fixed paraffin-embedded tissue, however, FISH analysis is more robust and exhibits a higher clinical sensitivity than RT-PCR.

Key Words: medallion-like dermal dendrocyte hamartoma, plaque-like CD34+ dermal fibroma, superficial (plaque-like) dermatofibrosarcoma protuberosans, CD34, COL1A1-PDGFB fusion gene

The spectrum of CD34-positive (CD34+) tumors of the skin comprises a heterogeneous family of mesenchymal neoplasms with multiple lines of differentiation, ranging from the fibroblastic to the hematopoetic lineage. Among these, most diagnostic difficulties are encountered within the group of dermal fibroctic spindle cell proliferations, some of which are poorly defined and present with a wide clinical and histomorphologic spectrum.

COL1A1-PDGFB-
Fibrous hamartoma of infancy

Fibroblastic connective tissue nevus

Medallion-like dendrocyte hamartoma

Plaque-like CD34+dermal fibroma

Fibrous hamartoma of infancy
• *Subdermal* fibromatous tumor in infants, present at birth in nearly 20% of cases
• Almost always a **solitary lesion**
• Striking predominance in **boys**
• **Painless solitary subcutaneous mass**
• Commonly involves the **axillary folds**, followed by shoulders and upper arms > upper trunk > groin >>> head and neck > distal extremities
• **Can reach 20 cm in diameter**

*may be very worrying for clinicians*
Subcutis
3 distinct components

- immature mesenchymatous tissue
- bands of (myo)fibroblastic fascicles
- islands of mature fat
• immature mesenchymatous tissue: stellate or primitive cells in a myxoid matrix
• fibroblastic fascicles resembling cells in fibromatoses
• islands of mature fat without lipoblasts
In about half of cases: pronounced sclerosing process with pseudo-angiectoid spaces
- slit-like spaces lined by flattened to prominent tumor cells
- occasional multinucleated cells
- strong positivity for CD34

**simulates Giant Cell Fibroblastoma**
In rare cases, focal nodules with:

- markedly elevated cellularity,
- high nuclear grade,
- brisk mitotic activity (Ki67 up to 100 %)

within an otherwise typical FHI

→ simulating Fibrosarcoma

**ETV6-NTRK3** -

*Al-Ibraheemi A.

- Landmark genetic finding: Epidermal Growth Factor Receptor (EGFR) exon 20 insertion/duplication mutations (12 cases)
- No spontaneous regression
- **Cured by local excision**
- Low recurrence rate *even with incomplete excision*....
Lipofibromatosis (infantile fibromatosis)

- First described by Fetsch et al. series of 45 cases
- Uncommon subcutaneous neoplasm
- Predominantly arises in infants. Unique to children
- Infiltrative and poorly defined firm mass, ranging from 2 to 7 cm in diameter
- Affects mainly the distal upper and lower extremities, less often the trunk, head and neck
- Frequently recurs after surgery
- Biphasic tumour confined to the subcutis

• Abundant mature adipose tissue traversed by well-defined interlacing fascicles
• Fascicles made up of bland short or elongated spindled cells
• Focal myxoid or collagenized areas
- Oval to spindled short fibroblasts
- Univacuolated adipocytes, adjacent to the fibrous septa (pseudo-lipoblasts)
• Fatty tissue may be prominent

Focal reactivity for SMA, CD34
Lipofibromatosis

Infantile fibromatosis

Fibrous hamartoma of infancy
Agaram et al.: a series of LPF-like cases

Rare, < 25 cases previously reported

Infants (several cases) to 38 years

Maximum dimension ranged from 1.3 to 8 cm

Wide anatomic distribution but lower extremities > upper extremities > head and neck regions

Locally aggressive behavior: high rate of local recurrences if incompletely excised

2016 Lipofibromatosis-like Neural Tumour

Recurrent NTRK1 Gene Fusions Define a Novel Subset of Locally Aggressive Lipofibromatosis-like Neural Tumors

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Abstract: The family of pediatric fibroblastic/myofibroblastic proliferations encompasses a wide spectrum of pathologic entities with overlapping morphologies and undefined genetic abnormalities. Among the superficial lesions, lipofibromatosis (LPF), composed of an admixture of adipose tissue and fibroblastic elements, in the past has been variously classified as infantile hemangioendothelioma or infantile fibromatous hamartoma of infancy. In disarray, we have encountered a group of superficial soft tissue tumors occurring in children and young adults, with a not infrequent growth pattern reminiscent of LPF, variable cytologic atypia, and a distinct immunoprofile of S100 protein and CD34 reactivity, suggestive of neural differentiation. S10X10 and melanocytic markers were negative in all cases tested. In contrast, a control group of classic LPF displayed bland, monomorphic histology and lacked S10 protein immunoreactivity. To define the pathogenetic abnormalities in these seemingly distinctive groups, performed RNA sequencing for fusion gene discovery in 2 cases each, followed by screening for any novel alterations identified in a larger cohort representing both entities. The 2 index LPF-like neural tumors (LPF-NNT) showed TP53- NTRK1 and TP53- NTRK1 gene fusions, which were further validated by fluorescence in situ hybridization (FISH) and reverse transcription polymerase chain reaction. Subsequent FISH screening of 14 LPF-NNT identified recurrent NTRK1 gene rearrangements in 6 of 14 (42.9%) cases. Of the NTRK1-negative LPF-NNT cases, 1 case each showed ROS1 and ALK gene rearrangements. In contrast, none of the 25 classic LPFs showed NTRK1 gene rearrangements, although regional abnormalities were noted in the LG2-22 region by FISH in a majority of cases. Furthermore, NTRK1 immunostaining was positive only in NTRK1 rearranged S100-positive LPF-NNT but negative in classic LPF. These results suggest that NTRK1 oncogenic activation through gene fusion defines a novel and distinct subset of soft tissue tumors resembling LPF, best displaying cytologic atypia and a neural immunoprofile, provisionally named LPF-like neural tumors.

Key Words: Lipofibromatosis, neural, NTRK1, TP53, LMNA

Pediatric fibroblastic/myofibroblastic mesenchymal neoplasms are a morphologically diverse group of often locally aggressive soft tissue tumors that encompass a wide spectrum of pathologic entities. Classification of these tumors has been controversial, due to their rare incidence, morphologic similarities, and similar clinical presentation overlapping with true sarcomatous processes, such as infantile fibromatosis, and spindle cell rhabdomyosarcoma. Aside from the more common and well-characterized desmoid-type fibromatoses, other pediatric lesions in this spectrum, including lipofibromatosis (LPF), classifying spocytic fibroma, and myofibromatosis, lack well-defined genetic abnormalities and are often diagnostically challenging. Apart from a single case report of LPF harboring a p49/9 translocation,† there are no other studies to date investigating their molecular alterations. Most LPFs affect young children and occur in the soft tissues of the trunk and extremities (hands and feet) and are characterized by a highly infiltrative growth pattern in the surrounding tissues. The extent of disease is often underestimated by preoperative imaging, leaving in most instances to incomplete excision and subsequent local recurrence. Immunohistochemically, they often show variable but inconsistent staining for CD34 and SMA and are negative for other diagnostic markers. We have encountered in our consultation practice a subset of lesions that resemble the growth pattern of LPF but show variable cytologic atypia and an immunoprofile more closely related to neural tumors, with positivity for S100 and CD34.

In an attempt further our understanding of the genetic alterations in these lesions, we sought to investigate tumors in the LPF morphologic spectrum by...
- Subcutis
- Infiltrative pattern mimicking that of LPF
- Spindle cells show fusiform nuclei with **mild nuclear atypia** and **hyperchromasia**
- No significant mitotic activity or necrosis
- **Extensive positivity for S100 protein**
- **CD34**: positivity ranging from focal to multifocal diffuse staining
- **SMA** variably +

IW Lao et al. Pathology 2018; 50(5): 519-523
- **NTRK1 rearrangement** (FISH) including: 
  - TPR-NTRK1, TPM3-NTRK1, LMNA-NTRK1 gene fusions
- **No NTRK1 rearrangements found in 25 cases of lipofibromatosis**

- Lipofibromatosis
- Low-grade MPNST
- Infantile fibrosarcoma
- DFSP

 Courtesy Marie Karanian

YP Hung et al. Histopathology 2018, 73: 634-644
• **Pan-TRK antibody**: highly sensitive for tumours which harbour NTRK3 and NTRK1 rearrangements
• may be a useful diagnostic adjunct
• not entirely specific but no false negatives
Lipofibromatosis

« Infantile fibromatosis »

Fibrous hamartoma of infancy

Lipofibromatosis-like neural tumor
Congenital/Infantile Fibrosarcoma

- Rare, occurs in the first year of life
- Relatively good prognosis
- Local recurrences, rare distant metastases
- Most deaths are related to early cataclysmic hemorrhage
- Characterized by the ETV6-NTRK3 fusion
- Elongated fascicles of highly atypical spindle cells +/- SMA +
- Numerous mitoses
- « herring-bone pattern »
- Slender stroma
Large angiomatous cavities that look like malformative structures
18 days

Punch biopsy

Lipofibromatosis or
Fibrous hamartoma of infancy
18 days

Punch biopsy

At 9 MO another punch biopsy

Lipofibromatosis or

Fibrous hamartoma of infancy

Lipofibromatosis

Fibrous hamartoma of infancy
18 days

Punch biopsy

Lipofibromatosis

Fibrous hamartoma of infancy

At 9 MO new punch biopsy

10 months

Excisionnal biopsy

Lipofibromatosis

Fibrous hamartoma of infancy
Congenital Infantile Fibrosarcoma Associated With a Lipofibromatosis-Like Component: One Train May Be Hiding Another

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Abstract: Congenital infantile fibrosarcoma (CIFS) is a soft tissue sarcoma of infants mainly involving lower extremities and usually developing during the first year of life. At another end of the spectrum of pediatric fibroblastic lesions, lipofibromatosis is a rare benign infiltrative soft tissue tumor that affects children. The authors report in this study a particular presentation with a CIFS surrounded by lipofibromatosis-like areas. The presence of a surrounding benign tumor confounded and delayed CIFS diagnosis.

Key Words: biopsy, sarcoma, congenital infantile fibrosarcoma, tumors, lipofibromatosis

(Am J Dermatopathol 2017;39:463–467)

INTRODUCTION

NTRK3 fusion transcript resulting from t(12;15) (p13;q25) translocation in most cases, but this transcript is nonspecific. It is frequently present in congenital hypercellular mesoblastic nephroma, mammary analog secretory carcinoma of salivary glands and secretory carcinoma of the breast, and in some leukemias. Tumor karyotype analysis may show chromosomal anomalies such as 8, 11, 17, and/or 20 trisomy. At another end of the spectrum of pediatric fibroblastic lesions, lipofibromatosis is a rare benign infiltrative soft tissue tumor of children. It presents as a painless, slowly growing mass of the subcutaneous tissue. Lipofibromatosis can develop antenatally in almost 20% of cases. On pathological sections, lipofibromatosis is characterized by lobules of mature adipose tissue within interlacing fascicles of fibroblasts with variable amounts of collagen. No malignant transformation of lipofibromatosis has been described so far.
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<th>LPF-like neural tumor</th>
<th>LPF</th>
<th>Low-grade MPNST</th>
<th>Infantile fibrosarcoma</th>
<th>DFSP</th>
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<td><strong>Atypia</strong></td>
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<td>Negative for NTRK1 rearrangement</td>
<td>Neurofibromin 1, PTEN, IGF1R, EGFR, MAPK</td>
<td>ETV6-NTRK3 fusion</td>
<td>91% with COL1A1-PDGFB fusion</td>
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<td><strong>Natural history</strong></td>
<td>Local recurrence with incomplete excision</td>
<td>Local recurrence with incomplete excision</td>
<td>Potential for distant metastasis, 50% with NF type 1</td>
<td>Potential for distant metastasis</td>
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VARS 2020 27th DERMSPATH & SKI RETREAT

From 19/01/2020 til 24/01/2020 Vars les Claux, Hautes Alpes, France, will host the 27th Dermatopathology and Ski Retreat. For many years Dermatologists and Pathologists from many countries have met in a friendly and unformal atmosphere. Teaching will be based upon slide seminars and lectures covering different fields of Dermatopathology. Participants are invited to present their own cases. Microscopes will be available. Of course Non Skiers are welcomed. They will enjoy walking in breath-taking panoramas, huskey rides and many other activities.

The meeting is limited to the first 40 registrants.

WHERE TO STAY?

The Escondus Hotel will host the meeting. You have to contact them to get a room there. You may also rent an apartment or a studio close to the Escondus. Many other hotels are available too. Please consult vars website or find opportunities at airbnb.

Contact: sylvie.fraitag@aphp.fr