

CASE REPORT

Low-fat, plexiform spindle cell lipoma of the lip expressing S100 protein: a neural tumor simulator

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Abstract

The plexiform variant of spindle cell lipoma is very uncommon. In fact, as far as we are aware only seven cases have been previously reported. We describe herein the case of a 49-year-old man with a smooth nodule of the mucosa of the lower lip that was gradually increasing. Surgical excision of the lesion was done and the study revealed the histological and immunohistochemical features of a plexiform spindle cell lipoma (PSCL). Peculiar to this case was the location in the lip, the presence of abundant S100-positive dendritic cells, and scarce mature lipogenic cells. S100 protein reactivity has rarely been observed in classical and plexiform spindle cell lipoma. To our knowledge, no case of PSCL displaying abundant S100-positive dendritic cells has been described. This feature may lead to a diagnostic pitfall. The main differential diagnosis includes the neuroma group, plexiform intraneural neurofibroma (PIN), plexiform schwannoma and plexiform hybrid tumor of perineurioma and cellular neurothekeoma. It is imperative correctly diagnose and differentiate PSCL from neural tumors because they may show syndromic associations, have different prognosis, including malignant transformation in PIN, and the management of all these lesions differs.

Keywords: plexiform spindle cell lipoma, plexiform schwannoma, plexiform neurofibroma, plexiform hybrid neural tumor, lip, oral cavity.

Introduction

Oral spindle cell lipoma (SCL) is rare, more common in women, and has a predilection for the tongue and cheek [1]. This tumor is exceptionally located in the lip. In fact, only three cases have been reported in this location [1–3]. Plexiform spindle cell lipoma (PSCL) is a very rare, distinctive variant of spindle cell lipoma that can cause diagnostic difficulties due to its uncommon frequency and pattern of growth. To our knowledge, only seven cases of this tumor have been reported to date [4].

We report herein the first case of a PSCL located in the mucosa of the lower lip. This tumor showed peculiarities uncommonly reported including scant mature fat cells and presence of abundant S100-positive dendritic cells. This rare variant of PSCL should be recognized because it can be misdiagnosed as a tumor of neural origin.

Case presentation

A 49-year-old male patient presented to our Department with a history of a slowly growing painless nodule involving the lower lip that had been noted for many years. He denied experiencing previous trauma at the affected area.

Physical examination revealed a nondescript smooth-surfaced, non-tender nodule measuring 1.5 cm located in the mucosa of the lower lip next to the left commissure. Minor salivary gland tumor was considered in the differential diagnosis.

The nodule was excised under local anesthesia. The postoperative period was uneventful. Fourteen months after surgery, he is well without recurrence of the lesion.

Pathological findings

The excised specimen measured 1.8×1×0.8 cm. The cut surface showed a vaguely nodular, white-yellow ill-defined mucosal lesion. Histopathological examination revealed a hypocellular plexiform neoplasm situated in the dermis (Figure 1A) and subcutaneous fat (Figure 1B). It was composed of multiple, discrete, crosscut round to oval nodules or longitudinally sectioned enlarged fascicles. They were separated from one another by variable fibrous or adipose tissue. Nodules and fascicles were interconnected and constituted by bland, haphazardly arranged, elongated cells with small, ovoid, or fusiform hyperchromatic nuclei enmeshed in a collagenized stroma. Nucleoli were inconspicuous. Cytoplasm was pink with no discernible cell membrane (Figure 2A). Scarce (<5%), single or in small clusters mature adipocytes irregularly arranged along the lesion were seen (Figure 2, A and B). Tumor cells were associated with wiry to thick hyalinized rope-like collagen bundles (Figure 3). Hypercellularity, nuclear palisades, cellular pleomorphism, necrosis, atypical mitotic figures, cystic degeneration, dilated vessels with thick hyaline walls, or small plexiform vascular proliferation were not present. No lipoblasts were seen. Loose textured component of Alcian blue-positive deposits were focally observed in some nodules and fascicles (Figure 4). A thin fibrous capsule was present in the

nodules or fascicles. Inflammatory infiltrates were not seen.

Immunopathological studies were carried out on formalin-fixed 4- μ m-thick paraffin-embedded tissue sections using the EnVision FLEX+ Visualization System (Dako, Agilent Technologies, SL, Las Rozas, Madrid, Spain). The immunohistochemical (IHC) reaction was performed using appropriate tissue controls for the antibodies utilized. For the retinoblastoma-binding protein-6 (RBBP-6), human testis sections were used as control. Automatic staining was performed on an Autostainer Link 48 (Dako, Agilent Technologies, SL, Las Rozas, Madrid, Spain). Antibodies used in the IHC study are detailed in Table 1.

Immunohistochemically, the non-adipocytic cells stained for CD34 and S100 protein. Thus, numerous spindle to dendritic cells showed positivity for CD34 (Figure 5). Most of these cells showed strong, diffuse positivity in both nucleus and cytoplasm for S100 protein and displayed dendritic appearance (Figure 6). Very scant isolated spindle cells were reactive for factor XIIIa. Negativity for RBBP-6, neurofilament protein, epithelial membrane antigen (EMA), glucose transporter-1 (GluT-1), claudin-1, Sox-10, melan-A, human melanoma black 45 (HMB45), D2-40, signal transducer and activator of transcription-6 (STAT-6), CD57, calretinin, and smooth muscle actin was observed in the lesion. The mature adipocytes displayed a thinned cytoplasmic rim positive for S100 protein.

Table 1 – Antibodies used in this study

Antibody	Source	Clone	Dilution	Retrieval solution pH (Dako)
CD34	Dako	QBEnd 10	FLEX RTU	High
Claudin-1	Abcam	Polyclonal	1:200	Low
GluT-1	Gene Tex	Polyclonal	1:50	Low
EMA	Dako	E29/EP1	FLEX RTU	High
Sox-10	Biocare Medical	BC34	1:100	High
S100 protein	Dako	Polyclonal	FLEX RTU	High
RBBP-6	Abcam	Polyclonal	1:100	High
Neurofilament protein	Dako	2F11	FLEX RTU	High
Factor XIIIa	Thermo Scientific	AC-1A1	Prediluted	High
Melan-A	Dako	A103	FLEX RTU	High
HMB45	Dako	HMB45	FLEX RTU	High
D2-40	Dako	D2-40	FLEX RTU	High
STAT-6	Abcam	Polyclonal	1:100	High
CD57	Dako	TB01	FLEX RTU	High
Calretinin	Dako	DAK-Calret 1	FLEX RTU	High
Smooth muscle actin	Dako	1A4	Flex RTU	High

GluT-1: Glucose transporter-1; EMA: Epithelial membrane antigen; RBBP-6: Retinoblastoma-binding protein-6; HMB45: Human melanoma black 45; STAT-6: Signal transducer and activator of transcription-6; Dako (Agilent Technologies, SL, Las Rozas, Madrid, Spain); Abcam, Cambridge, UK; Gene Tex, Irvine, CA, USA; Biocare Medical, Concord, CA, USA; Thermo Scientific, Waltham, MA, USA; RTU: Ready-to-use.

The patient had no stigmata of mucosal neural syndrome, neurofibromatosis or schwannomatosis.

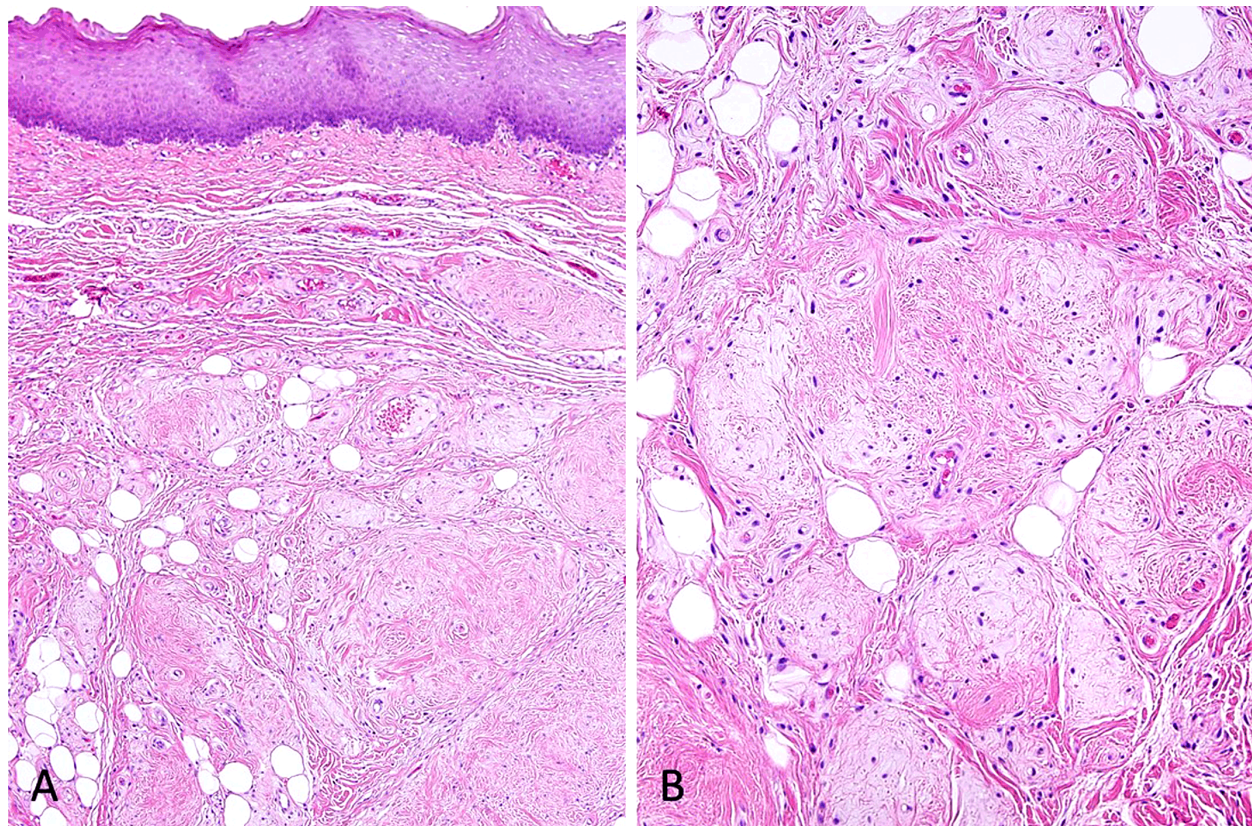


Figure 1 – Microscopic features of the tumor: (A) Labial mucosa showing round to oval nodules of varying size in the lamina propria; (B) Labial hypodermis – the nodules are composed of compact and loose hypocellular tissue. Hematoxylin–Eosin (HE) staining: $\times 100$ (A); $\times 200$ (B).

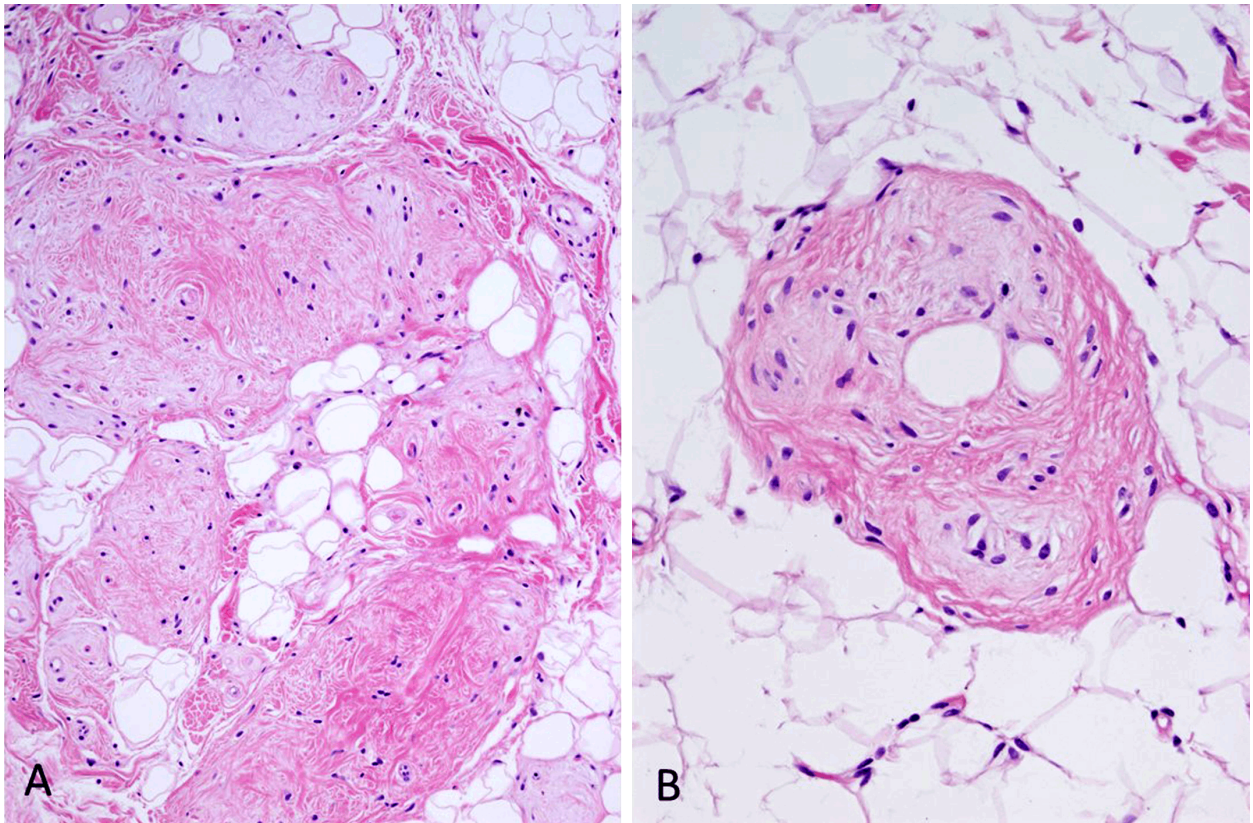


Figure 2 – Microscopic features of the tumor: (A) Scant mature adipocytes can be seen in the nodules and fascicles; (B) Two isolated mature fat cells are present in a tumor nodule. HE staining: $\times 200$ (A); $\times 400$ (B).

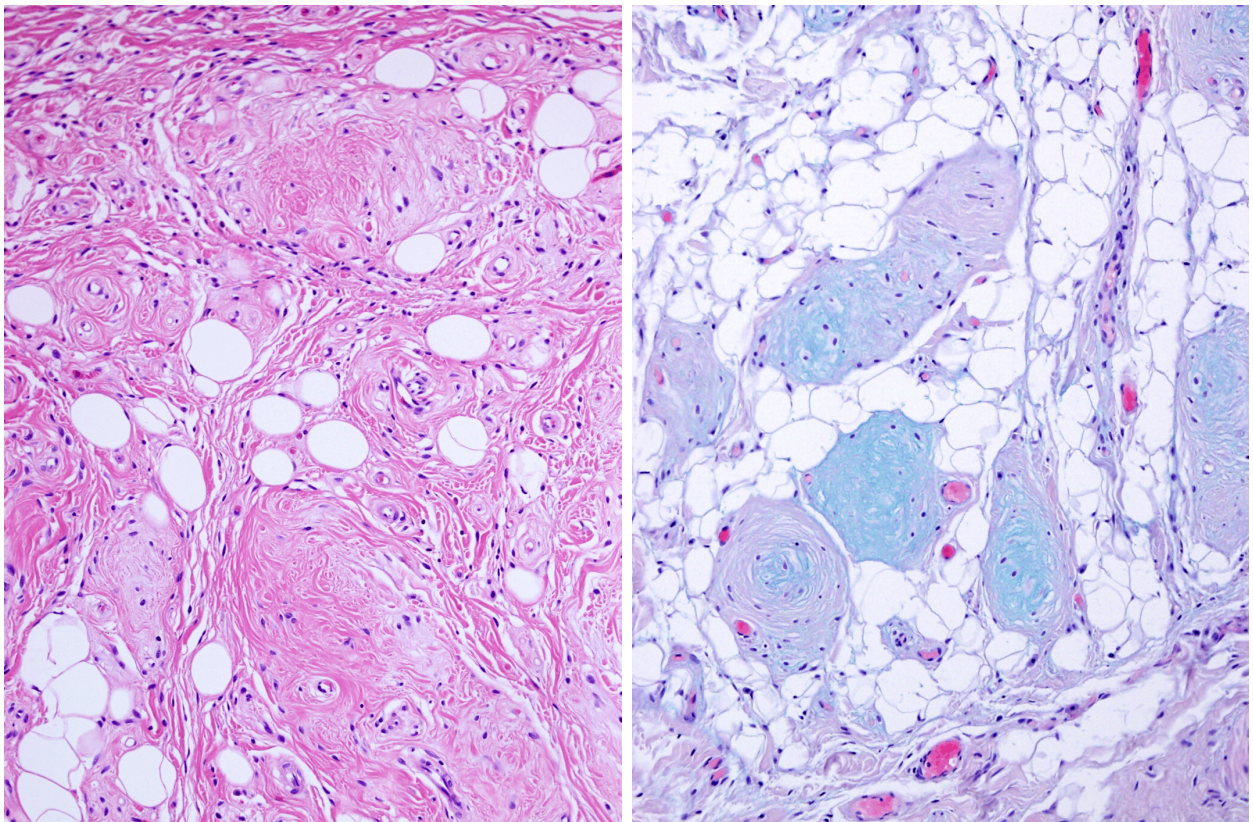


Figure 3 – The stroma is predominantly collagenous. Characteristic wiry to ropey collagen can be seen in the nodules and fascicles (HE staining, $\times 200$).

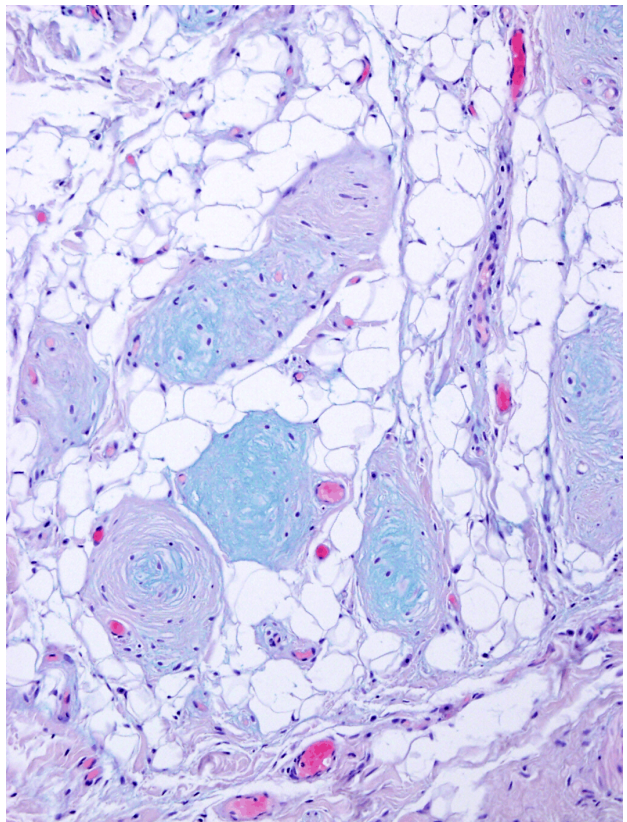


Figure 4 – Alcian blue-positive deposits are focally observed in tumor nodules and fascicles ($\times 200$).

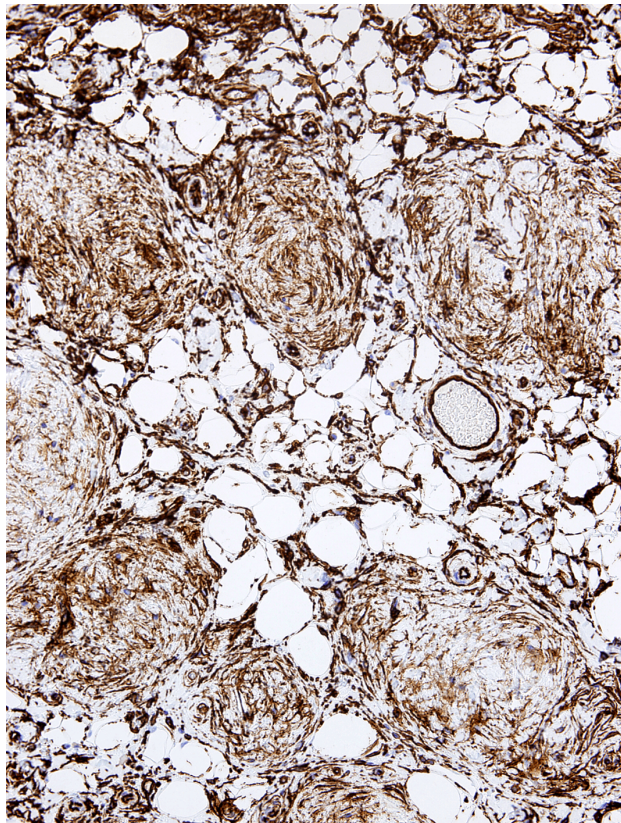


Figure 5 – Abundant number of spindle and dendritic cells positive for CD34 are present in the nodules and fascicles ($\times 200$).

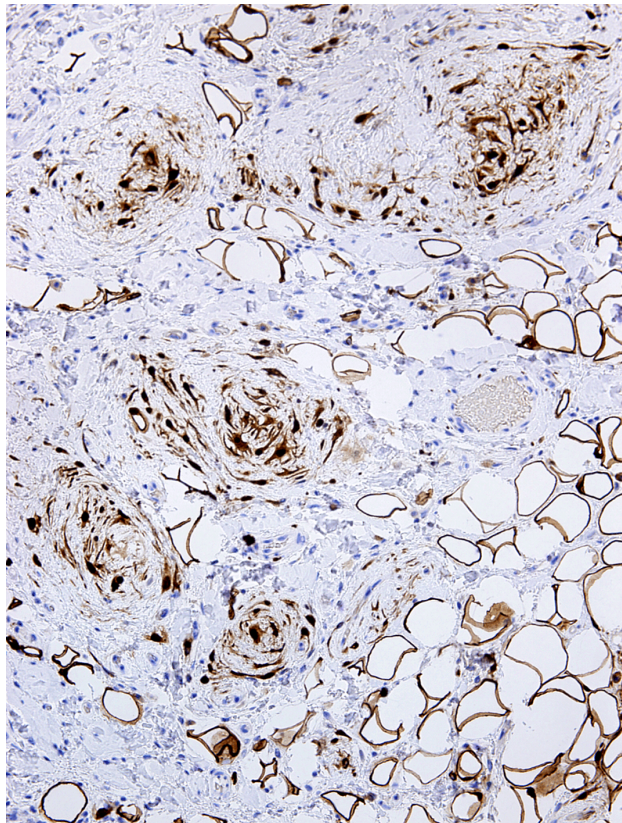


Figure 6 – Non-fat tumor cells displaying strong and diffuse S100 positivity. Both nucleus and cytoplasm of these cells are reactive for the antibody. Most cells have dendritic morphology. Mature adipocytes display a thinned cytoplasmic rim positive for S100 protein ($\times 200$).

Discussions

SCL represents 1.7% to 5% of oral lipomas [2, 5]. The average size of these lesions (0.8 cm) is smaller than their non-oral counterparts. They are more common in women and show preference for the tongue and cheek. The mean age at diagnosis is 63.6 years with a range between 31 and 88 years [1]. As far as we are aware, only three cases of lip SCL have been reported. Billings *et al.* [1] reported of a 55-year-old female (lower lip, 0.6 cm), Manor *et al.* [2] of a 23-year-old male (upper lip, 2.4 cm), and Girgis & Cheng [3] of a 38-year-old female patient (lower lip, 0.6 cm).

PSCL is a rare tumor. Only seven cases have been reported previously. The age of the patients ranged from 32 to 58 years with a mean of 45.7 years. There were five females and two males. Most cases were located in the thigh-groin-buttock area. No case was observed in the oral cavity or in the lip [4].

Spindle cell adenolipomas are categorized separately [6–8] and they are not included in the present discussion.

Microscopically, the PSCL shows interconnected nodules and fascicles that consist of bland, non-lipogenic, CD34-positive, spindle-shaped cells, mature fat cells, and hyalinized thick rope-like collagen fibers in a collagenous or myxoid matrix. Our case showed the following two peculiarities: (i) presence of abundant number of S100 positive dendritic cells in both compact and loose textured areas, and (ii) very scant fat cells. Both features are infrequent and represent a diagnostic challenge.

Diffuse, strong expression of S100 protein by spindle-shaped cells of classical SCL with nuclear and cytoplasmic location has been reported [9]. These cells were also present in 25% of cells in a case of PSCL [4]. In the present case, most cells showed a dendritic morphology. Thus, our tumor shares the dendritic morphological feature with dendritic fibromyxolipoma (DFML) [10–13]. However, the dendritic cells of DFML are no reactive for S100 protein. On the other hand, DFML is considered a rare variant of SCL [12]. The ratio of the non-lipogenic cells and mature adipocytes in SCL is variable, but the majority of cases have significant proportions of both components. When the number of fat cells is scarce (<5%), the case can be diagnostically challenging [14]. However, identification of other typical characteristics of SCL are key features to the diagnosis of low-fat SCL. Occasionally, desmin may be expressed in 16% of spindle cells and B-cell lymphoma 2 (Bcl2) in 56% of SCL [15]. Factor XIIIa may also be positive in some spindle cells of SCL [16] and PSCL [4]. Mentzel *et al.* [9] consider that non-fat-storing mesenchymal cells of SCL are immature cells showing a variable immunophenotype and capable of different lines of differentiation.

Our lesion fulfills histopathological and IHC criteria for the diagnosis of lip PSCL, such as bland non-lipogenic, CD34-positive spindle cell component, mature adipocytes, characteristic wiry to ropey collagen, negativity for retinoblastoma protein, and fascicular and plexiform pattern of growth. Spindle cell lipomas show deficient

nuclear expression of retinoblastoma protein by immunohistochemistry [17]. These tumors are characterized by deletions of chromosome 13q, often with loss of 16q [18]. The RB1 gene is located within the deleted region of chromosome 13.

The main differential diagnosis includes the neuroma group, and other plexiform tumors including plexiform intraneural neurofibroma (PIN), plexiform schwannoma (PS) and plexiform hybrid tumor of perineurioma and cellular neurothekeoma (PHTPCN). Neuroma group, embracing traumatic-, multinodular palisaded encapsulated-, or multiple mucosal-neuroma, shows abundant axons, Schwann and perineurial cells, and CD34-positive endoneurial fibroblasts. Thus, these lesions show the whole components of a nerve. In addition, a parent nerve may be observed. Mucosal neuromatosis is a marker of multiple endocrine neoplasia type IIb [19]. The lips are a common site of involvement. PIN shows increased endoneurial, myxoid, Alcian blue-positive substance, centrally situated dense cores of neurofilament protein-positive nerve fibers, Schwann cells, endoneurial fibroblasts and perineurial sheaths surrounding the affected fascicles. Thus, this lesion displays multiple cellular types. The lesion is rarely located in the lips [20]. It is important to differentiate PSCL from PIN because PSCL follows a benign clinical course with complete surgical excision being curative, whereas PIN is associated with neurofibromatosis type 1 and carries a risk of malignant transformation. Very few cases of PS affecting the lips have been reported [21, 22]. PS is a tumor exclusively composed of Schwann cells and usually exhibits an intraneural growth. Some lesions show Antoni B areas and nuclear palisades or Verocay body formation. The interconnected nodules and fascicles most commonly are surrounded by a thin capsule of perineurium. Scant neurofilament protein+ axons are sometimes found. PS may show syndromic associations in 10% of cases, most commonly neurofibromatosis type 2 and schwannomatosis [23, 24] 5% each [24]. PHTPCN seems to have a special predilection for the lips [23]. The lesion is composed of nests of tumor cells embedded in a myxoid stroma. Cells are organized in a storiform and lamellar pattern. Immunohistochemically, they show intense, diffuse positivity for S100A6, microphthalmia-associated transcription factor (Mitf), NKI/C3, protein gene product 9.5 (PGP9.5), EMA, and neuron-specific enolase (NSE); and weaker, focal reactivity for CD34, claudin-1, and GluT-1. Thus, this neoplasm is considered a benign nerve sheath tumor with hybrid features of perineurioma and cellular neurothekeoma [25, 26].

✉ Conclusions

PSCL is an uncommon distinctive benign tumor rarely located in the lip. The tumor may show partial overlapping immunoprofile with dermal neural tumors. Thus, this lesion can present a diagnostic challenge to the unwary pathologist. The neoplasm is worthy of recognition because neural tumors may show syndromic associations, have different prognosis, and the management of all these lesions differs.

Conflict of interests

The authors declare that they have no conflict of interests.

Consent

Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

References

- [1] Billings SD, Henley JD, Summerlin DJ, Vakili S, Tomich CE. Spindle cell lipoma of the oral cavity. *Am J Dermatopathol*, 2006, 28(1):28–31.
- [2] Manor E, Sion-Vardy N, Joshua BZ, Bodner L. Oral lipoma: analysis of 58 new cases and review of the literature. *Ann Diagn Pathol*, 2011, 15(4):257–261.
- [3] Girgis S, Cheng L. Rare occurrence of lip spindle cell lipoma. *Case Rep Oncol Med*, 2015, 2015:382925.
- [4] Val-Bernal JF, Hermans S. Dermal plexiform spindle cell lipoma. *Rom J Morphol Embryol*, 2016, 57(2 Suppl):875–878.
- [5] Naruse T, Yanamoto S, Yamada S, Rokutanda S, Kawakita A, Takahashi H, Matsushita Y, Hayashida S, Imayama N, Morishita K, Yamashita K, Kawasaki G, Umeda M. Lipomas of the oral cavity: clinicopathological and immunohistochemical study of 24 cases and review of the literature. *Indian J Otolaryngol Head Neck Surg*, 2015, 67(Suppl 1):67–73.
- [6] Kazakov DV, Spagnolo DV, Kacerovska D, Kempf W, Michal M. Cutaneous adenolipoma: extending the spectrum of changes in the lipomatous and epithelial components. *Am J Dermatopathol*, 2011, 33(1):56–59.
- [7] Wilk M, Zelger BG, Zelger B. Adenolipoma-eccrine and apocrine variants with evidence for a hamartomatous process. *Am J Dermatopathol*, 2013, 35(1):138–141.
- [8] AbdullGaffar B, Raman LG, Prince S. Dermal spindle cell adenolipoma. *Am J Dermatopathol*, 2014, 36(6):527–529.
- [9] Mentzel T, Rütten A, Hantschke M, Hornick JL, Brenn T. S-100 protein expressing spindle cells in spindle cell lipoma: a diagnostic pitfall. *Virchows Arch*, 2016, 469(4):435–438.
- [10] Suster S, Fisher C, Moran C. Dendritic fibromyxolipoma: clinicopathologic study of a distinctive benign soft tissue lesion that may be mistaken for a sarcoma. *Ann Diagn Pathol*, 1998, 2(2):111–120.
- [11] Zhang XJ, Zhou S, Nie K, Chen DF, Kui GJ, Zhang XH. Dendritic fibromyxolipoma in the right inguinal and perineum regions: a case report and review of the literature. *Diagn Pathol*, 2013, 8:157.
- [12] Wong YP, Chia WK, Low SF, Mohamed-Hafiah NH, Sharifah NA. Dendritic fibromyxolipoma: a variant of spindle cell lipoma with extensive myxoid change, with cytogenetic evidence. *Pathol Int*, 2014, 64(7):346–351.
- [13] AlAbdulsalam A, Arafah M. Dendritic fibromyxolipoma of the piriform sinus: a case report and review of the literature. *Case Rep Pathol*, 2016, 2016:7289017.
- [14] Billings SD, Folpe AL. Diagnostically challenging spindle cell lipomas: a report of 34 “low-fat” and “fat-free” variants. *Am J Dermatopathol*, 2007, 29(5):437–442.
- [15] Tardío JC, Aramburu JA, Santonja C. Desmin expression in spindle cell lipomas: a potential diagnostic pitfall. *Virchows Arch*, 2004, 445(4):354–358.
- [16] Silverman JS, Tamsen A. Fibrohistiocytic differentiation in subcutaneous fatty tumors. Study of spindle cell, pleomorphic, myxoid, and atypical lipoma and dedifferentiated liposarcoma cases composed in part of CD34+ fibroblasts and FXIIIa+ histiocytes. *J Cutan Pathol*, 1997, 24(8):484–493.
- [17] Chen BJ, Mariño-Enríquez A, Fletcher CDM, Hornick JL. Loss of retinoblastoma protein expression in spindle cell/pleomorphic lipomas and cytogenetically related tumors: an immunohistochemical study with diagnostic implications. *Am J Surg Pathol*, 2012, 36(8):1119–1128.
- [18] Dal Cin P, Sciot R, Polito P, Stas M, de Wever I, Cornelis A, Van Den Berghe H. Lesions of 13q may occur independently of deletion of 16q in spindle cell/pleomorphic lipomas. *Histopathology*, 1997, 31(3):222–225.
- [19] O’Riordain DS, O’Brien T, Crotty TB, Gharib H, Grant CS, van Heerden JA. Multiple endocrine neoplasia type 2B: more than an endocrine disorder. *Surgery*, 1995, 118(6):936–942.

- [20] Zwane NP, Noffke CE, Raubenheimer EJ. Solitary oral plexiform neurofibroma: review of the literature and report of a case. *Oral Oncol*, 2011, 47(6):449–451.
- [21] Lobo I, Torres T, Pina F, Dominguez M, Alves R, Barbas do Amaral J, Selores M. Plexiform schwannoma of the lip mucosa. *J Eur Acad Dermatol Venereol*, 2009, 23(5):616–618.
- [22] Dhua S. A rare case of plexiform schwannoma of the lower lip: treatment and management. *Indian J Plast Surg*, 2015, 48(2):208–211.
- [23] Berg JC, Scheithauer BW, Spinner RJ, Allen CM, Koutlas IG. Plexiform schwannoma: a clinicopathologic overview with emphasis on the head and neck region. *Hum Pathol*, 2008, 39(5):633–640.
- [24] Val-Bernal JF, Figols J, Vázquez-Barquero A. Cutaneous plexiform schwannoma associated with neurofibromatosis type 2. *Cancer*, 1995, 76(7):1181–1186.
- [25] Requena L, Sitthinamsuwan P, Fried I, Kaddu S, Schirren CG, Schärer L, Hantschke M, Cerroni L, McCalmont TH, Kutzner H. A benign cutaneous plexiform hybrid tumor of perineurioma and cellular neurothekeoma. *Am J Surg Pathol*, 2013, 37(6): 845–852.
- [26] Yamada S, Kitada S, Nabeshima A, Noguchi H, Sasaguri Y, Hisaoka M. Benign cutaneous plexiform hybrid tumor of perineurioma and cellular neurothekeoma arising from the nose. *Diagn Pathol*, 2013, 8:165.

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