J Cutan Pathol 2009: 36: 381–384
doi: 10.1111/j.1600-0560.2008.01038.x
Blackwell Munksgaard. Printed in Singapore

Journal of
Cutaneous Pathology

Clear cell fibrous papule: report of a case mimicking a balloon cell nevus

Clear cell fibrous papule (FP) is a rare variant of FP. We report a 39-year-old female patient who presented with a dome-shaped papule on the nose. The diagnosis of clear cell FP was made based on histological and immunohistochemical studies. Interestingly, scattered S-100 cells were admixed within the lesion, a finding hitherto not reported. The S-100 positivity may be misleading and should be cautiously interpreted.

Chiang Y-Y, Tsai H-H, Lee W-R, Wang K-H. Clear cell fibrous papule: report of a case mimicking a balloon cell nevus.
J Cutan Pathol 2009; 36: 381–384. © Blackwell Munksgaard 2008.

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Accepted for publication March 25, 2008

Fibrous papule (FP) is a common skin lesion mainly found on the face of an adult. The classical presentation is a solitary, flesh-color, dome-shaped papule on the nose. Histologically, it is an angiofibroma that is consistent with the picture of a group of lesions, including adenoma sebaceum, pearly penile papules and angiofibromas in other syndromes. Immunohistochemically, the cells of FP stain positively with CD68 and factor XIIIa, but do not express S-100 protein, suggesting a fibrohistiocyte and dendritic cell origin. In addition to the ordinary type, several histological variants of FP have been described, including clear cell, hypocellular, pigmented, pleomorphic, inflammatory, granular cell and epithelioid variants.[1,2] We herein report a new case of clear cell FP, which unusually displays patchy S-100 positivity.

Case report

A 39-year-old female presented with a flesh-colored to semitranslucent papule on her nose for a duration of 5 months (Fig. 1A). On physical examination, this asymptomatic skin lesion was dome shaped with a smooth surface, measuring about 0.3 cm in diameter. The clinical impression was an intradermal nevus. A punch biopsy was performed on the lesion.

The biopsy specimen showed proliferation of clear cells in the fibrotic dermis. The nuclei of the clear cells were small, round or scalloped. There was no hyperchromasia or mitotic figures (Fig. 1B). Some spindle, stellate and round cells were admixed in the lesion as well as moderate, patchy lymphocytic infiltrates (Figs 1B and 2C). Dilated vascular channels in the fibrous stroma were also seen. On Fontana-Masson stain, increased melanin pigments were noted along the basal layer. Mucicarmine and periodic acid-Schiff (PAS) stains were negative on these clear cells. Immunohistochemically, vimentin (Dako, Carpinteria, CA, USA) was diffusely and strongly positive (Fig. 1C), and factor XIIIa (Novocastra, Newcastle Upon Tyne, UK) labeled most of the vacuolated and stromal cells (Fig. 1D). CD68 (Dako) labeled the upper portion of the tumor, especially the large clear, vacuolated cells (Fig. 2). S-100 protein (Dako) was focally positive on some of the smaller vacuolated and other stromal cells (Fig. 3). CD1a (Novocastra) labeled some dendritic cells in the dermis as well as the epidermal Langerhans cells, but those vacuolated cells labeled with S-100 appeared to be negative. NKI/C3 (Novocastra),

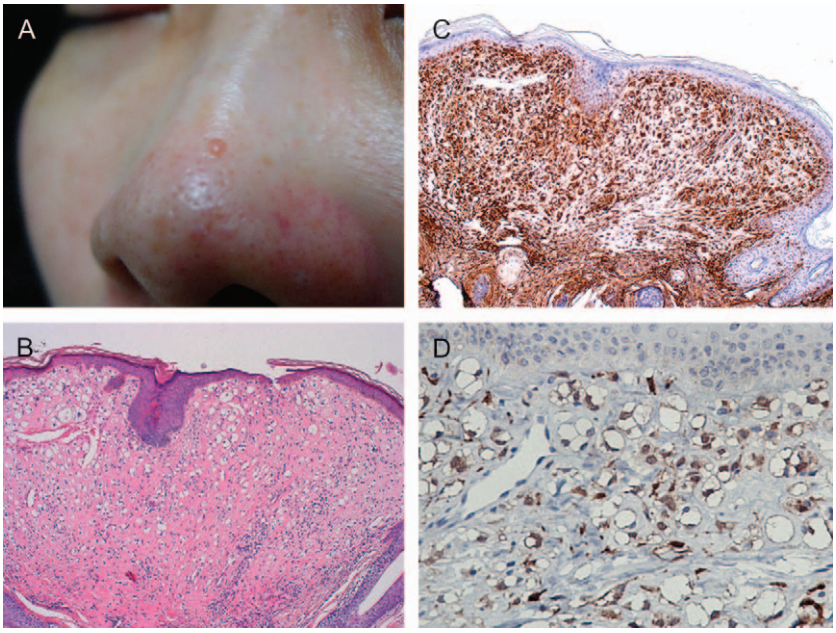

Fig. 1. A) A dome-shaped, well-defined flesh-colored to slightly translucent papule on the nose. B) The histology shows a lesion composed of clear cells in the upper dermis, admixed with round and spindle cells. The lesion is relatively symmetric with infiltration of lymphocytes at the base and periphery (hematoxylin and eosin, original magnification ×100). C) Diffuse positive staining for vimentin (original magnification ×100). D) Factor XIIIa is mostly positive on both balloon cells and stromal cells (original magnification ×400).

HMB-45 (Dako), cytokeratin (Dako; clone: AE1/AE3), epithelial membrane antigen (EMA) (Dako) and CD34 (Dako) were all negative.

Of the immunohistochemical stains, S-100 protein was performed first as an ancillary stain, and the lesion was interpreted as a balloon cell nevus originally. A series of markers were then performed to differentiate other clear cell tumors. The final diagnosis was a clear cell FP after the panel of histological and immunohistochemical studies.

Discussion

FP is a benign skin lesion commonly found on the face, first reported by Graham in 1965.[4] The histology is that of an angiofibroma. It shows dermal fibroplasia with proliferation of spindle-shaped, stellate or multinucleate stromal cells. The blood vessels are increased and some are ectatic. The epidermis often shows flattening of rete ridges and hyperplasia of melanocytes. In the 1970s, it was believed that the FP was a regressing nevocellular nevus of the nasal region because of the following features: the increased number of melanocytes and melanin pigment in the basal layer and the simulation of the stellate stromal cells with the spindle cells in Spitz nevus.[3,4] However, electron microscopic studies and improved immunohistochemical studies indicated that the tumor cells showed features of dermal dendritic cells and fibroblasts/histiocytes. Therefore, it is now generally agreed that FP is a form of an angiofibroma rather than a regressing nevus.[5–7]

The clear cell FP is a rare variant of FP. Only 18 cases have been reported thus far[1,6,8,9] [Soyer (9 cases), Lee (6 cases), Bansal (2 cases), Rose (1 case)]. This variant of FP was first described by Soyer et al. in the English literature. In their series, vimentin was positive in all nine cases and CD68 and factor XIIIa were only focally positive on the vacuolated or clear cells. S-100, cytokeratin and EMA were negative.[8] Ultrastructurally, the lesional cells showed the presence of multilobate nuclei and absence of desmosomal structures, melanosomes and basement membranes, thereby favoring the fibrocytic origin of these clear cells.

Initially, the lesion was diagnosed as a balloon cell nevus, which is an important differential diagnosis. Clinically, balloon cell nevus presents as an asymptomatic papule usually located on the head, neck and trunk, although it can also be found on the mucosal areas such as conjunctiva, soft palate and pharynx. Under the hematoxylin and eosin stain, balloon cell nevus can be undistinguishable from a clear cell FP, but the nuclei of balloon cell nevus are more centrally located and more rounded compared with those of clear cell FP. Balloon cell melanoma usually has an architectural derangement, larger nuclei and mitoses in the dermis. Immunohistochemically, balloon cell nevus is diffusely positive for S-100, while clear cell FP is mostly negative. Other differential diagnoses of a clear cell tumor on the face include xanthoma, sebaceous neoplasm, granular cell tumor and metastatic renal cell carcinoma. Xanthoma cells can be labeled with CD68, but their cytoplasm has a foamy appearance. Sebaceous tumors contain lipids and are EMA positive. Granular cell tumors contain pink, granular cytoplasm rather than clear cytoplasm. They are PAS and S-100 positive. The negative staining result of cytokeratin can exclude metastatic renal cell carcinoma from the differential diagnosis.

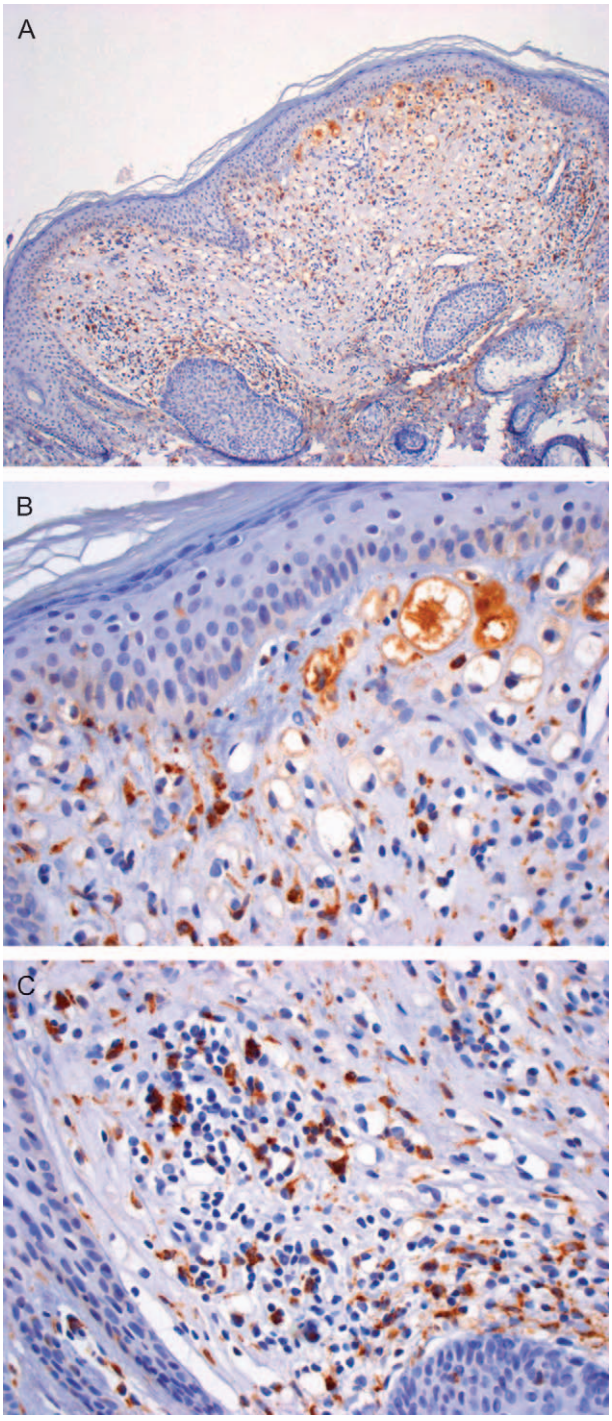

Fig. 2. A–C) Positive staining for CD68 is seen in the large vacuolated cells. Note the smaller spindle and stellate cells with dendrites are also positive. A) ×100, B) ×400 and C) ×400.

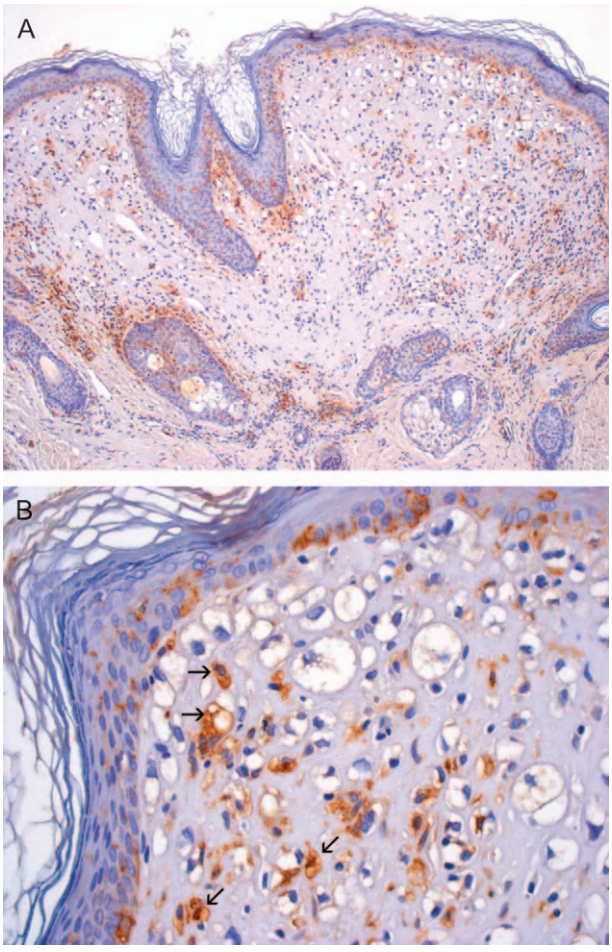

Fig. 3. A and B) Positive staining for S-100 is seen in the some of smaller vacuolated cells and the round, nevus-like cells (indicated by arrows). The large balloon cells were negative. Note the positive staining of epidermal melanocytes and Langerhans cells. A) ×100 and B) ×400.

Although FP is considered of fibrohistiocytic or dermal dendritic cell origin based on its vimentin and factor XIIIa positivity, the origin of the clear cells in its clear cell variant is still obscure. In Soyer's and Lee's series, factor XIIIa was only focally positive in clear cell FP.[6,8] NKI/C3, a lysosomal antigen, was found to be positive in all six cases by Lee et al.[6] This case, however, showed that factor XIIIa labeled most lesional cells, whereas NKI/C3 was negative.

In our case, besides the typical manifestation of clear cell FP, it also shows focal positive staining of S-100 on the smaller vacuolated cells and some nevus-like cells. S-100 positivity is an extremely rare finding in the ordinary FP and has never been reported in clear cell variant. In 1983, Spiegel et al. studied 20 cases of FPs and found no S-100 staining within the stellate cells or was this protein found in the mesenchymal cells with some features of nevus cells.[5] Cerio et al. found three lesions with increased S-100-positive cells, especially in the upper dermis, in a study of 25 cases, while most lesions were positive for factor XIIIa and negative for S-100.[10] They concluded that FP is mainly a proliferation of factor XIIIa-positive dermal dendritic cells, but there is some evidence that a small percentage of cells may be of melanocytic origin (involuted nevi). The two large series of clear cell FP found that neither clear cells nor stromal cells

stained with S-100.[6,8] In our case, the clear cell that labeled S-100 did not express CD1a, excluded the possibility of these cells being Langerhans cells. The explanation for the nature of these S-100-positive cells remains uncertain. An interpretation is that it represents dermal dendritic cells (or transformed Langerhans cells), which are derived from the hematopoietic cells and may be present in certain microenvironment. Another possibility is that they are melanocytes, raising the possibility of a historical view of a regressing (balloon cell) nevus. The contrast staining results of NKI/C3 and factor XIIIa of the clear cells among different reports of clear cell FP imply the possible heterogeneity of these clear cells. Further studies are warranted to elucidate the nature of the clear cell FP as well as the scattered S-100 cells within the lesion.

In conclusion, we present a case of clear cell FP that mimics balloon cell nevus. This finding may add difficulty to the differential diagnosis of this rare variant of FP. A complete immunohistochemical study may be necessary to avoid misdiagnosis and inappropriate treatments.

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