Title

Adult-onset reticulohistiocytoma presenting as a solitary asymptomatic red knee nodule: report and review of clinical presentations and immunohistochemistry staining features of reticulohistiocytosis

Journal

Dermatology Online Journal, 20(3)

Authors

Cohen, Philip R
Lee, Robert A

Publication Date

2014

DOI

10.5070/D3203021725

Volume 20 Number 3
March 2014

Case Report

Adult-onset reticulohistiocytoma presenting as a solitary asymptomatic red knee nodule: report and review of clinical presentations and immunohistochemistry staining features of reticulohistiocytosis

Philip R. Cohen MD and Robert A. Lee MD PhD

Dermatology Online Journal 20 (3): 3

Division of Dermatology, University of California San Diego, San Diego, California.

Correspondence:

Philip R. Cohen, MD
10991 Twinleaf Court
San Diego, CA 92131-3643
mitehead@gmail.com

Abstract

Reticulohistiocytomas are benign dermal tumors that usually present as either solitary or multiple, cutaneous nodules. Reticulohistiocytosis can present as solitary or generalized skin tumors or cutaneous lesions with systemic involvement and are potentially associated with internal malignancy. A woman with a solitary red nodule on her knee is described in whom the clinical differential diagnosis included dermatofibroma and amelanotic malignant melanoma. Hematoxylin and eosin staining and immunoperoxidase studies of the biopsy specimen established the diagnosis of adult-onset reticulohistiocytoma (solitary epithelioid histiocytoma). Reticulohistiocytoma is characterized by mononuclear, and occasionally multinuclear, histiocytes with eosinophilic "glassy" cytoplasm. The immunohistochemical profile of a reticulohistiocytoma demonstrates consistent positive expression for CD68 (a marker that is expressed by histiocytes but can also show positive staining in melanomas and carcinomas), CD163 (a very specific marker for histiocytes), and vimentin. Reticulohistiocytomas show variable positive expression for MITF (microphthalmia transcription factor) and S100 protein, both of which are more commonly used as markers for melanocytes. Recurrence of a reticulohistiocytoma is rare, even for patients with an incompletely removed lesion. However, our patient elected to have her residual tumor completely excised.

Key Words: adult, asymptomatic, cutaneous, diffuse, epithelioid, histiocytoma, knee, multicentric, nodule, onset, red, reticulohistiocytoma, reticulohistiocytosis, solitary

Introduction

Reticulohistiocytomas are benign dermal tumors that usually present as either solitary or multiple, cutaneous nodules. They consist of mononuclear, and occasionally multinuclear, histiocytes with eosinophilic "glassy" cytoplasm. We describe a woman with a solitary adult-onset reticulohistiocytoma appearing as a red nodule on her knee, review the clinical presentations of reticulohistiocytosis, and summarize the immunohistochemistry staining features of these tumors.

Case synopsis

A 28-year-old woman presented with an asymptomatic, recently noted and enlarging, lesion on her left knee. She is a hemophilia carrier and has epilepsy that is well controlled on levetiracetam (Keppra, 500 mg twice daily). She also daily takes folic acid (Folvite, 1 mg) and norethindrone-ethinyl estradiol 1-20 (Microgestin 1/20). Her mother had a melanoma on the left arm at age 45 years that was successfully treated with wide local excision; there was no recurrence over the last 10 years.

Cutaneous examination showed a painless firm red 5 x 5 mm nodule on the medial aspect of the left knee (Figure 1). The clinical differential diagnosis included a dermatofibroma and an amelanotic malignant melanoma.

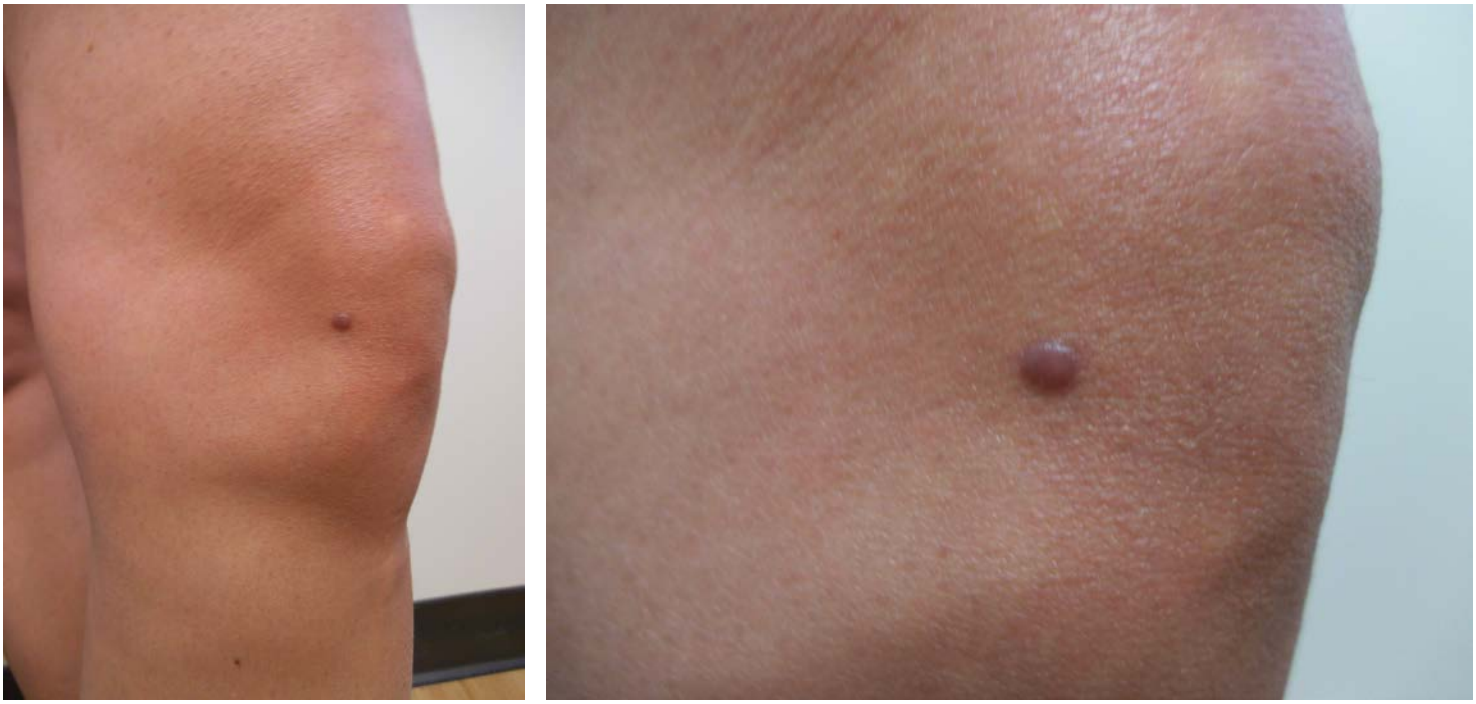

Figure 1a and 1b. Distant (a) and closer (b) views of an asymptomatic red nodule on the left distal knee

Hematoxylin and eosin stained sections show a dermal proliferation of epithelioid cells; some of the tumor cells have eosinophilic "glassy" cytoplasm whereas others have smudgy gray cytoplasm. Multinucleated giant cells are present. Surrounding the tumor cells is a mixed inflammatory infiltrated consisting of neutrophils, eosinophils, and lymphocytes. Rare mitoses are noted in the epithelioid cells (Figure 2).

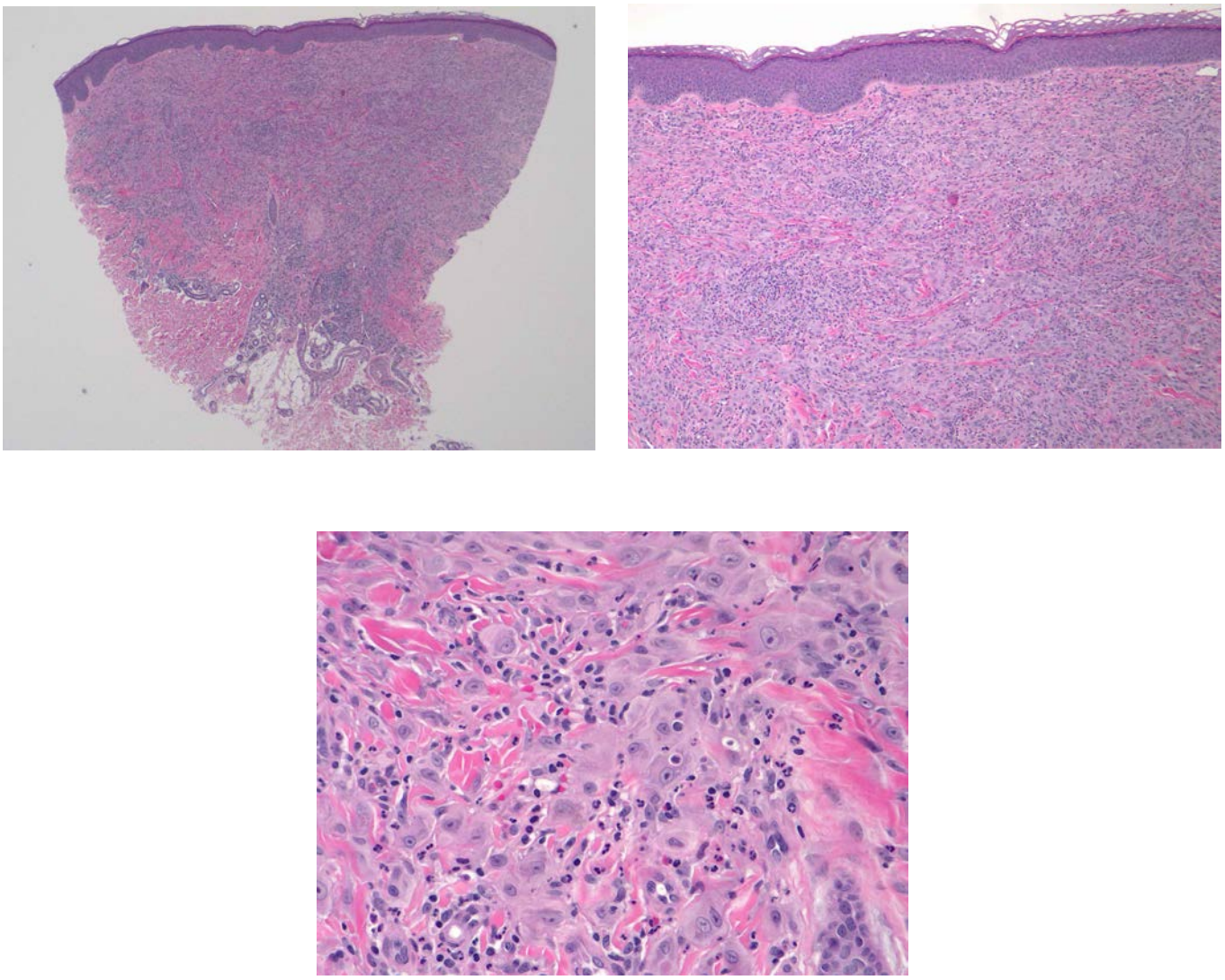

Figure 2a, 2b, and 2c. Low (a), medium (b), and high (c) magnification views; Low magnification shows a diffuse infiltration of tumor cells in the dermis. Medium magnification shows a mixed inflammatory infiltrate of neutrophils, eosinophils, and lymphocytes amongst the tumor cells. High magnification shows the epithelioid tumor cells with abundant smudgy, pink to gray, cytoplasm (hematoxylin and eosin, a = X2, b = X10, c = X40).

Immunoperoxidase stained sections show that some of the epithelioid cells stain positively for S100 protein (Figure 3); in addition, microphthalmia transcription factor (MITF) highlights both the nucleus and cytoplasm in a significant portion of the tumor cells (Figure 4). The epithelioid cells also demonstrate diffuse positive staining for CD68 (Figure 5) and CD163 (Figure 6). The epithelioid tumor cells do not stain for CD1a, cytokeratin AE 1/3, MART-1, or tyrosinase.

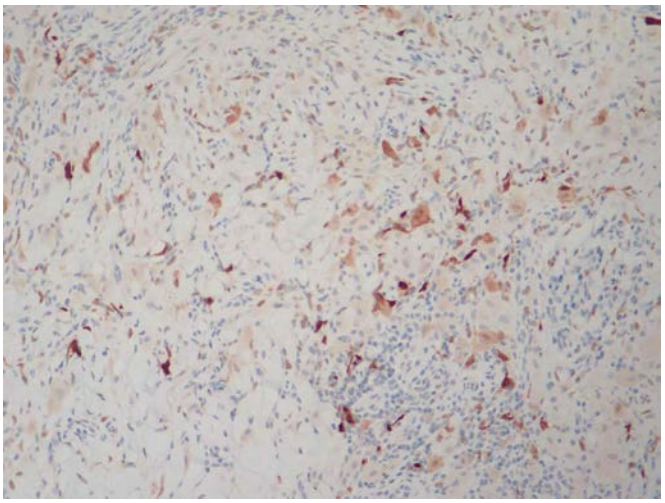

Figure 3. Occasional epithelioid tumor cells show strong cytoplasmic staining for S100 (immunoperoxidase, X20).

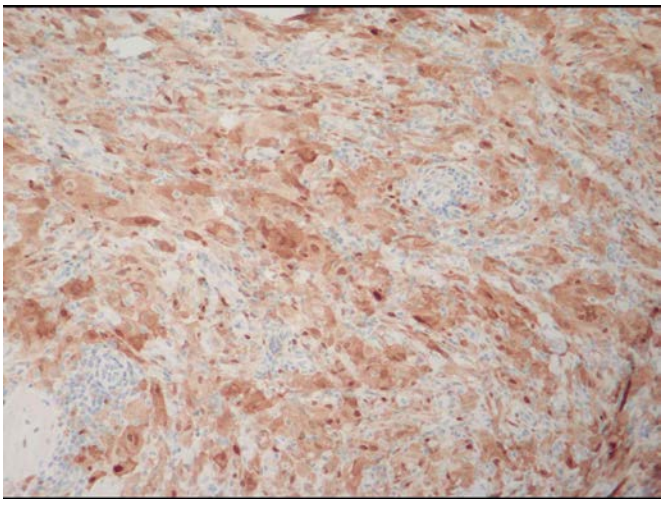

Figure 4. Diffuse and stong nuclear and cytoplasmic staining of tumor cells for MITF (immunoperoxidase, X20)

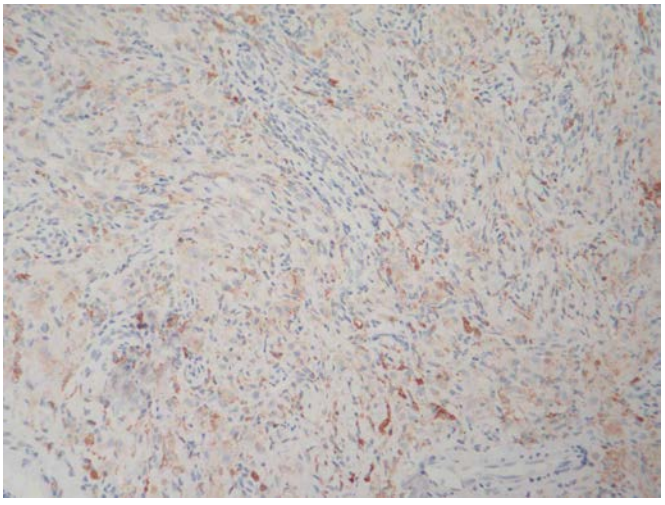

Figure 5. Diffuse and light cytoplasmic staining of tumor cells for CD68 (immunoperoxidase, X20)

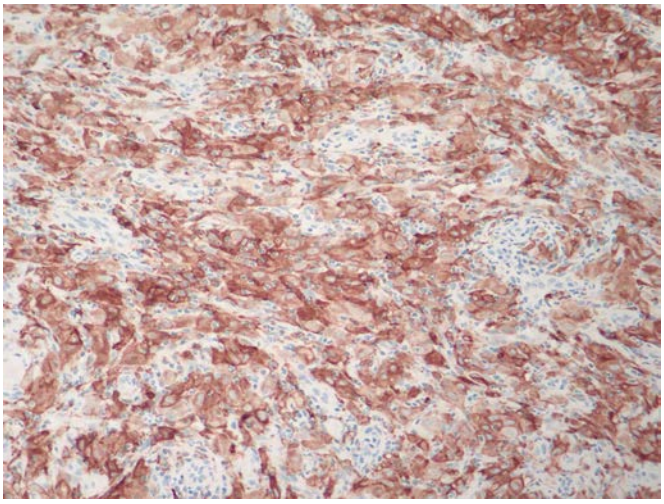

Figure 6. Diffuse and strong cytoplasmic staining of tumor cells for CD163 (immunoperoxidase, X20)

Correlation of the clinical presentation, hematoxylin and eosin stained sections, and the immunohistochemistry studies established the diagnosis of adult-onset reticulohistiocytoma (solitary epithelioid histiocytoma).

Discussion

Reticulohistiocytosis can present in 3 clinical settings (Table 1) [1-9]. Multicentric reticulohistiocystosis describes the occurrence of numerous cutaneous reticulohistiocytomas, frequently presenting as nodules on the hands and face, with an accompanying symmetric arthritis. In addition, multicentric reticulohistiocytosis can be a cutaneous paraneoplastic syndrome; an associated internal malignancy has been discovered in 15% to 31% of these patients [5,7,9]. Albeit less commonly, diffuse cutaneous reticulohistiocytosis, in which there are generalized reticulohistiocytomas of the skin without systemic involvement, has also been observed [5,8]. Rarely, the onset of either multiple reticulohistiocytomas [7,10] or a solitary lesion [6] has also been associated with pregnancy..

Table 1. Reticulohistiocytosis: clinical presentation

Clinical presentation	References
Cutaneous only	
Solitary [a]	1-7
Generalized [b]	5,8
Cutaneous with systemic involvement	
Multicentric [c]	4,5,7,10

[a] The term reticulohistiocytoma was coined by Zak [4] to describe a cutaneous lesion without any related systemic illness. To more appropriately acknowledge the cytomorphology and immunophenotype, Miettinen and Fetsch proposed to refer to the individual lesion as a solitary epithelioid histiocytoma [3]. [b] Diffuse cutaneous reticulohistiocytosis presents with generalized reticulohistiocytomas of the skin without any systemic involvement. [c] There is a potential association with internal malignancy.

Reticulohistiocytoma of the skin was originally described by Zak in 1950 [4]. The lesion appears as a dermal nodule and consists of large histiocytes with eosinophilic “glassy” cytoplasm. Subsequently, in 2006, Miettinen and Fetsch [3] recommended to rename the lesion as a “solitary epithelioid histiocytoma” based on the 1997 classification of histiocytic disorders proposed by the Histiocyte Society [11]. Currently, both terms are used when reporting patients with a single lesion [1,2].

The largest series of patients with a solitary reticulohistiocytoma included 44 individuals: 26 men and 18 women with a median age of 35 years (range = 2.5 to 74 years) at the time of diagnosis. The reticulohistiocytoma was noted to typically present as an asymptomatic superficial, circumscribed, mildly elevated, cutaneous or mucosal papule or nodule. In this study, the lesions were located on the trunk (16 tumors) leg (12 tumors), head and neck (8 tumors including 2 intraoral), arm (6 tumors), and penis (1tumor); the site was not provided for 1 patient [3].

Subsequent investigators have also observed a reticulohistiocytoma located on either the penis [2] or the eyelid [1]. The nodule size can range from a few millimeters to 2 cm in diameter [9] and their appearance has been described as flesh-colored [1], gray-white [3], red-brown [5,7], tan [5], yellowish [2,3,6], or yellow-brown [5]. Our patient’s lesion was red.

The clinical differential diagnosis for a solitary dermal nodule is diverse. Submitted diagnoses with biopsy specimens have included basal cell carcinoma, cyst, dermatofibroma, hemangioma, juvenile xanthogranuloma, granuloma, keratoacanthoma, molluscum contagiosum, melanocytic nevus, pyogenic granuloma, rheumatoid nodule, squamous cell carcinoma, and xanthoma [3,5]. The appearance of our patient's red nodule raised the morphologic possibility of an amelanotic malignant melanoma.

A reticulohistiocytoma shows a well-circumscribed dermal tumor consisting of a dense infiltrate of mononuclear and occasional multinuclear histiocytes. Most of the tumor cells are large epithelioid histiocytes with eosinophilic "glassy" cytoplasm located in the upper dermis and extending into the mid dermis. Vacuolated, spindle-shaped and xanthomatized mononuclear histiocytes can also be present. An associated mixed inflammatory infiltrate of lymphocytes and neutrophils is also typically present. Mild nuclear atypia may be noted and mitotic activity is low or absent (median of 1 mitosis per 10 high power fields; range = 0 to 4 mitoses per 10 power fields) [3,5].

Immunohistochemistry studies of reticulohistiocytoma are summarized in Table 2 [2,3,5]. The large epithelioid histiocytes are consistently positive for vimentin and histiocyte markers such as CD68 and CD163 [12,13]. Variable positive expression of the tumor cells, demonstrated by erratic and focal staining, for markers that are more commonly associated with melanocytic lesions (such as S100 protein and MITF) can also be observed [14]. When present, as in our patient, these findings can potentially be misleading and need to be interpreted as part of a panel of immunohistochemistry studies in order to establish the correct histiocytic lineage of the tumor cells. Keratinocyte (cytokeratin), Langerhans cell (CD1a), and certain melanocyte (Melan-A/MART-1, HMB-45, and tyrosinase) markers uniformly do not show any expression [2,3,5].

Table 2. Immunohistochemistry profile of reticulohistiocytoma

Immunoperoxidase stain expression	Reference
Consistent positive expression [a]	
CD68	3
CD163	3
Vimentin	3
Variable positive expression [b]	
MITF	3
S100 protein	3
No expression [c]	
CD1a	3
Cytokeratin	3
HMB-45	3
Melan-A/MART-1	2
Tyrosine	

Abbreviations: CD=cluster of differentiation, HAM56=macrophage marker; HMB=human melanoma black; Ki-67=a cellular marker for proliferation; KiM1P=pan macrophage marker; LCA=leukocyte common antigen; MART-1=melanoma antigen recognized by T-cells-1; Melan-A=MART-1; MITF=microphthalmia transcription factor; S100=the protein is 100% soluble in ammonium sulfate at neutral pH

[a] Expression of the following antigens are also usually positive: alpha-1-antitrypsin, HAM56, KiM1P, and lysozyme [6]. [b] The variable positive expression is demonstrated by erratic and focal staining; CD31 and CD45 (LCA) show delicate membrane staining in some cases. [c] When evaluated, very low Ki-67 index (<1) may be observed [2].

Our patient's asymptomatic red nodule prompted amelanotic malignant melanoma to be included in the clinical differential diagnosis. Hence, in order to characterize the origin of the large epithelioid tumor cells observed on hematoxylin and eosin stained sections, immunohistochemistry studies included stains that are usually markers for melanocytes (S100 protein and MITF), which were both positive. However, histiocytes can demonstrate positive expression for markers usually associated with melanocytes (S100 and MITF), keratinocytes (cytokeratin AE 1/3 which was negative), and histiocytes (CD68 which was positive). CD68 expression is not definitive and can also be observed in melanoma and carcinomas. Additional studies using other melanocyte markers (MART-1 and tyrosinase) were negative, excluding the possibility of an amelanotic malignant melanoma. A confirmatory study using a very specific marker for histiocytes (CD163 which was positive) established that the CD68 expression of the tumor cells represented a histiocyte lineage. The absence of CD1a expression excluded a Langerhans cell histiocytosis [12-14].

Conclusion

Adult-onset reticulohistiocytoma (solitary epithelioid histiocytoma) is uncommon. There is a substantial clinical differential diagnosis for a single dermal nodule and a biopsy may be necessary to establish the diagnosis. Reticulohistocytomas contain large epithelioid tumor cells in the dermis with eosinophilic "glassy" cytoplasm. Immunoperoxidase studies can be helpful to establish the expression of antigens associated with histiocyte origin. However, as in our patient, the immunoperoxidase results can be misleading when the histiocytic tumor cells also express some of the antigens more commonly associated with melanocytes. Although recurrence of a reticulohistiocytoma is rare, even for patients with an incompletely removed lesion, our patient elected to have her residual tumor completely excised.

References

1. Jakobiec FA, Kirzhner M, Tollett MM, Mancini R, Hogan RN: Solitary epithelioid histiocytoma (reticulohistiocytoma) of the eyelid. Arch Ophthalmol 2011;129:1502-1504. [PMID = 22084226]
2. Mannan AA, Kahvic M, Singh NG, Zahir M: Solitary epithelioid histiocytoma (reticulohistiocytoma) of the glans penis. Int Uol Nephrol 2012;44:1345-1348. [PMID = 22777481]
3. Miettinen M, Fetsch JF: Reticulohistiocytoma (solitary epithelioid histiocytoma). A clinicopathologic and immunohistiochemical study of 44 cases. Am J Surg Pathol 2006;30:521-528. [PMID = 16625100]
4. Zak FG: Reticulohistiocytoma ('ganglioneuromma') of the skin. Br J Dermatol 1950;62:351-355. [No PMID]
5. Zelger B, Cerio R, Soyer HP, Misch K, Orchard G, Wilson-Jones E: Reticulohistiocytoma and multicentric reticulohistiocytosis. Am J Dermatopathol 1994;16:577-584. [PMID = 7864294]
6. Hunt SJ, Shin SS: Solitary reticulohistiocytoma in pregnancy: immunohistochemical and ultrastructural study of a case with unusual immunophenotype. J Cutan Pathol 1995;22:177-181. [PMID = 7560354]
7. Oliver GF, Umbert I, Winkelmann RK, Muller SA: Reticulohistiocytoma cutis—review of 15 cases and an association with systemic vasculitis in two cases. Clin Exp Dermatol 1990;15:1-6. [PMID = 2311271]
8. Vazquez-Bayo MC, Rodriguez-Bujaldon A, Jimenez-Puva R, Galan M, Velez A, Morena JC, Romero A, Marchal T: Diffuse cutaneous reticulohistiocytosis. Actas Dermosifiliogr 2006;97:118-121. [PMID = 16595113]
9. Luz FB, Gaspar AP, Kalil-Gaspar N, Ramos-e-Silva M: Multicentric reticulohistiocytosis. J Eur Acad Dermatol Venereol 2001;15:524-531. [No PMID]
10. Conaghan P, Miller M, Dowling JP, Cowen P, Littlejohn G: A unique presentation of multicentric reticulohistiocytosis in pregnancy. Arthritis Rheum 1993;36:269-272. [PMID = 8431218]
11. Favara BE, Feller AC, Pauli M, Jaffe ES, Weiss LM, Arico M, Bucsky P, Egeler RM, Elinder G, Gadner H, Gresik M, Henter JI, Imashuku S, Janka-Schaub G, Jaffe R, Ladisch S, Nezelof C, Pritchard J: Contemporary classification of histiocytic disorders. The WHO committee on histiocytic/reticulum cell proliferations. Reclassification working group of the histiocyte society. Med Pediatr Oncol 1997;29:157-166. [PMID = 9212839]
12. Lau SK, Chu PG, Weiss LM: CD163. A specific marker of macrophages in paraffin-embedded tissue samples. Am J Clin Pathol 2004;122:794-801. [PMID = 15491976]
13. Nguyen TDT, Schwartz EJ, West RB, Warnke RA, Arber DA, Natkunam Y: Expression of CD 163 (hemoglobin scavenger receptor) in normal tissues, lymphomas, carcinomas, and sarcomas is largely restricted to the monocyte/macrophage lineage. Am J Surg Pathol 2005;29:617-624. [PMID = 15832085]
14. Ohsie SJ, Sarantopoulos GP, Cochran AJ, Binder SW: Immunohistochemical characteristics of melanoma. J Cutan Pathol 2008;35:433-444. [PMID = 18399807]