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# Malignant histiocytosis of the skin: a case report and review of the literature

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## Abstract

**Background:** Malignant histiocytosis is a rare neoplasm composed of abnormal histiocytes typically affecting the liver, spleen, lymph nodes, and bone marrow. This entity has been rarely documented involving the skin and has never been reported confined to the skin.

**Main Observations:** A 74-year-old white man presented to the dermatology clinic with complaints of a non-healing ulcerated lesion on his cheek of several months duration. Histopathological examination revealed a poorly circumscribed neoplasm consisting of pleomorphic epithelioid cells with abundant foamy cytoplasm. Immunohistochemistry was positive for CD-43, CD-68, and lysozyme, but negative for CD-3, CD-20, CD-30, CD-34, SMA, CD-1a or S-100. The prominent CD-68 and lysozyme staining along with the histological features, the clinical presentation of erythematous nodules with diffuse erythematous plaques, and absence of bone marrow findings, led to the diagnosis of malignant histiocytosis confined to the skin.

**Conclusion:** Malignant histiocytosis involving the skin is rare. The presence of large pleomorphic epithelioid cells with foamy cytoplasm, with or without engulfed erythrocytes should alert the dermatopathologist to the possibility of malignant histiocytosis. Appropriate immunohistochemical evaluation, including CD-43, CD-68, CD-1a, S-100, and lysozyme, should be completed to confirm the diagnosis.

## Introduction

Histiocytes are cells of the immune system that do not circulate within the vascular system, but rather remain stationed within tissue, where they function to eradicate foreign material. An increased number of these cells is referred to as histiocytosis. Malignant histiocytosis is a rare neoplasm composed of abnormal histiocytes typically affecting the liver, spleen, lymph nodes, and bone marrow. This entity has been rarely documented involving the skin and has never been reported confined to the skin.

## Case Report

A 74-year-old white man presented to the dermatology clinic for routine follow-up. The patient had a history of multiple non-melanoma skin cancers treated with excision and several condylomas in the preceding three years. He complained of a non-healing lesion on his cheek of several months duration. He denied fever, chills, night sweats, nausea, vomiting, and weight loss. On his right cheek, there was a 1 cm indurated, ulcerated erythematous papule. The clinical differential diagnosis included basal cell carcinoma, squamous cell carcinoma, and atypical fibroxanthoma. A 3 mm punch biopsy of the lesion was performed. Microscopic evaluation revealed a collection of dyshesive, large, epithelioid cells with abundant foamy cytoplasm confined to the dermis (Fig. 1). Scattered atypical mitotic figures were observed. The cytoplasm contained rare phagocytosed red blood cells. Immunohistochemistry revealed cells positive for lysozyme (Fig. 2), CD-43, CD-68 (KP-1), and negative for CD-3, CD-20 (L26), CD-30 CD-34, CD-1a (Fig. 3) and S-100. These results are consistent with malignant histiocytosis. A full physical exam was performed and similar cutaneous lesions were discovered along with widely distributed erythematous plaques, involving the trunk, arms and thighs. Six additional random biopsies of these lesions showed identical histological findings with an accompanying

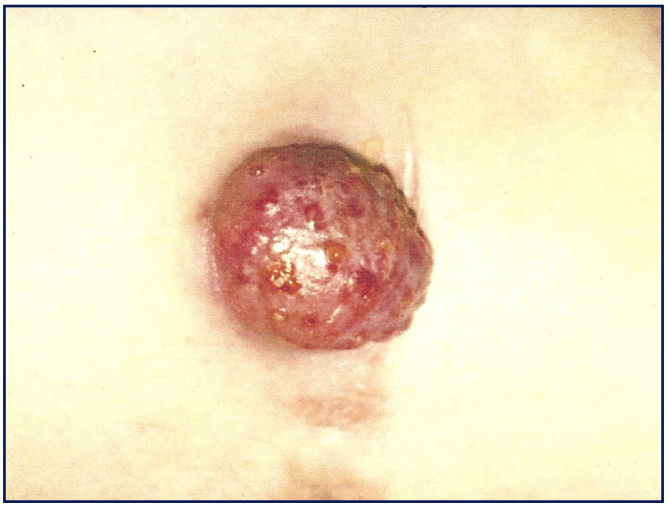

**Figure 1**
*Collection of large epithelioid cells with abundant foamy cytoplasm in the dermis (H&E, 400x). Clinical view of the nodule in lower right corner.*

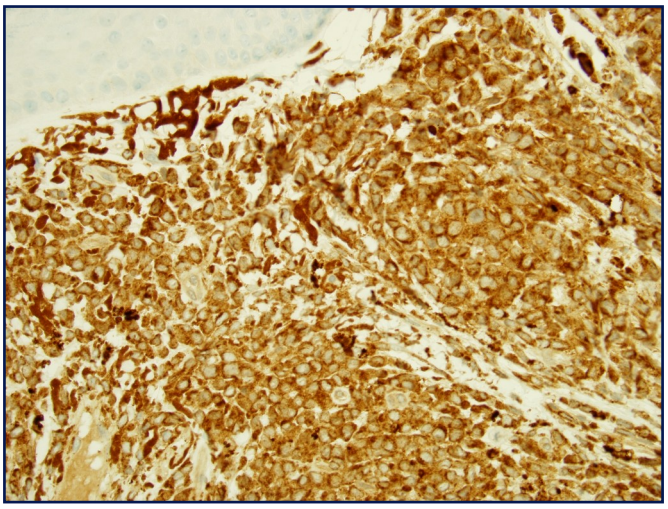

**Figure 2**
*Cells immunostaining positively for lysozyme (400x).*

immunostaining pattern similar to the initial biopsy. Following the diagnoses, a bone marrow biopsy was performed with flow cytometry showing a mild monocytosis with no clonal gene rearrangements nor other abnormalities. Peripheral blood analysis was within normal limits including a hemoglobin of 12 mg/dl and a white blood cell count of 7.5 x 109 L with an unremarkable smear. Follow-up nine months later revealed an increase number of similar cutaneous lesions without systemic symptoms and repeat bone marrow biopsy with flow cytometry was still normal. This signifies that malignant histiocytosis was confined to the skin.

## Discussion

Malignant histiocytosis (MH or histiocytic sarcoma) is a rare disease characterized by infiltration of normal tissue with abnormal histiocytes.[1-4] The WHO defines histiocytic sarcoma, with malignant histiocytosis being a subset,

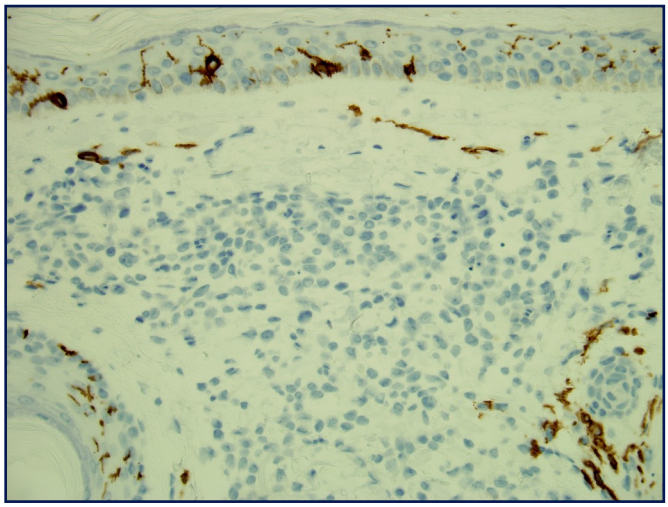

**Figure 3**
*Cells immunostaining negative for CD-1a (400x).*

as a malignant proliferation of cells showing morphologic and immunophenotypic features similar to those of mature tissue histiocytes with one or more histiocytic markers without dendritic markers, ex. CD1a and S100.[5] It typically is systemic in nature and pursues an aggressive course that may lead to death within a few weeks to months after onset of symptoms.[6] Patients may present with fever, malaise, weight loss, lymphadenopathy, hepatosplenomegaly, pancytopenia, and leukocytosis. Organs affected include the liver, spleen, lymph nodes, and bone marrow.[7] Skin involvement is uncommon (10-15%), but is rarely the presenting symptom.[6-13] Skin lesions are typically erythematous, maculopapular and can progress to papular or nodular lesions, with purpura, scaling and/or ulceration.[7,9,11,12] The male to female ratio is 2-3.5 : 1.[11] Histologically, MH is composed of numerous round, oval and polygonal shaped cells. The abundant cytoplasm of these cells appears foamy, eosinophilic and sometimes contains erythrocytes. The nuclei are multilobed with prominent nucleoli. Numerous mitotic figures can sometimes be found. The histiocytes infiltrate into the deep dermis and/or subcutaneous tissues and are concentrated around adnexal structures and blood vessels.[10] Patients afflicted with this condition vary in age with a range of 2 months to 90 years reported.[11] An aggressive chemotherapy regimen is usually employed and radiotherapy may be used for cutaneous lesions.[9]

The topic of malignant histiocytosis remains contentious. Historically, many cases originally diagnosed as malignant histiocytosis have been reclassified as large cell lymphoma, undifferentiated carcinoma, Hodgkin disease and malignant fibrous histiocytoma among other entities.[9,14,15] Pileri *et al.* has examined the topic of tumors of histiocytes and accessory dendritic cells providing insight into the topic and its nosologic designation, sui generis.[1] They defined MH as a neoplasm comprised of large, ovoid cells with eccentric nuclei and prominent nucleoli showing rare erythrophagocytosis. The mitotic count can be high and necrosis is often present. Immunostaining for

CD-68 and lysozyme are diffusely positive with rare examples of S-100, CD1a, CD21, CD35, CNA.42, CD34, MPO, CD3, CD20, CD79a, and CD30 immunopositivity.[1] The most important entity to exclude from MH is anaplastic large cell lymphoma (ALCL). ALCL and malignant histiocytosis are similar morphologically and, unlike malignant histiocytosis, ALCL typically involves the skin. With immunohistochemical analysis, many cases formerly classified as malignant histiocytosis were found to express Ki-1 (CD 30), a cytokine proliferation marker found in ALCL variants. The lymphocytic nature of these cases was further confirmed with genetic analyses of T-cell and B-cell surface receptor rearrangement studies.[16] An important foil cited for the high incidence of false diagnoses is the findings of histiocyte proliferation and histiocytes with erythrophagocytic activity, that often accompany cutaneous ALCL.[17] One group of investigators re-examined seven cases originally diagnosed as malignant histiocytosis using monoclonal antibodies to determine cell lineage. Only one of the patients was re-classified with malignant histiocytosis. The remainder had a reactive histiocytes with the malignancy being from T-cell origin.[18]

A final entity germane to dermatopathology to be considered in the differential diagnosis is entity Langerhans cell histiocytosis (LCH). LCH more commonly presents in the pediatric setting yet can present in accord with systemic involvement as a widespread cutaneous eruption. LCH generally possesses a uniform histology consisting of loose aggregates of histiocytes possessing grooved nuclei, intermediate cells, macrophages, T-cells, eosinophils and giant histiocytes.[19] Older lesions may show lower cellularity and fibrosis. In contrast to malignant histiocytosis, immunohistochemistry of the lesional cell in LCH will be positive for CD-1a, S-100 and CD-4 and variably positive for CD-68, lysozyme, and alpha-1 antitrypsin.[20] This dichotomy in antibody staining should permit differentiation of LCH from MH in most instances.

Scrutiny of the dermatologic literature yields few cases of malignant histiocytosis presenting in the skin using restrictive criteria as defined by Pileri *et al.*[1] (a malignant neoplasm of histiocytes, positive for one or more histiocytic markers but negative for accessory/dendritic cell markers).[1,6,13] Several cases in the past have also been diagnosed as such, but do not adhere to the latest criteria and/or lack the appropriate immunostaining techniques.[7,11,14,15] To the best of our knowledge, this is the first case reported that adheres to Pileri's criteria yet does not show evidence of systemic involvement.

## Conclusion

Malignant histiocytosis has historically been a challenging diagnosis for dermatopathologists, particularly due to its rarity in the skin. Our case and review of the literature showed that with the proper immunohistochemical staining regimen (CD-43, CD-68, CD-3, CD-20, CD-30, CD-34, lysozyme, CD-1a, and S-100) this disease entity can be readily distinguished from its counterparts.

## References


1. Pileri SA, Grogan TM, Harris NL, Banks P, Campo E, Chan JK, Favera RD, Delsol G, De Wolf-Peeters C, Falini B, Gascoyne RD, Gaulard P, Gatter KC, Isaacson PG, Jaffe ES, Kluin P, Knowles DM, Mason DY, Mori S, Müller-Hermelink HK, Piris MA, Ralfkiaer E, Stein H, Su IJ, Warnke RA, Weiss LM. Tumours of histiocytes and accessory dendritic cells: an immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases. *Histopathology*. 2002; 41: 1-29.
2. Rappaport H. Tumors of the hematopoietic system. Atlas of tumor pathology. 1966; Fasc. 8, Sect. 3(AFIP): 49-63.
3. Schmidt D. Malignant histiocytosis. *Curr Opin Hematol*. 2001; 8: 1-4.
4. Stone MS, Tschen JA. Malignant histiocytosis. *Cutis*. 1985; 36: 42-44.
5. Elaine S. Jaffe NLH, Harald Stein, James W. Vardiman. Tumours of the Haematopoitic and Lymphoid Tissues. World Health Organization Classification of Tumours; 2001. p. 278-279.
6. Akiyama M, Inamoto N, Nakamura K. Malignant histiocytosis presenting as multiple erythematous plaques and cutaneous depigmentation. *Am J Dermatopathol*. 1997; 19: 299-302.
7. Harper JI, Henry K, Mobayen M, Staughton RC. Malignant histiocytosis presenting with skin ulceration. *J R Soc Med*. 1982; 75: 982-984.
8. Caksen H, Kendirci M, Kandemir O, Patiroglu T. A case of malignant histiocytosis associated with skin involvement mimicking kwashiorkor. *Pediatr Dermatol*. 2001; 18:545-546.
9. Lahoti NG, Natarajan A, Karuna R, D'Souza RE. Cutaneous histiocytic lesions: a clinical dilemma. *J Postgrad Med*. 2000; 46: 275-277.
10. Newman B, Hu W, Nigro K, Gilliam AC. Aggressive histiocytic disorders that can involve the skin. *J Am Acad Dermatol*. 2007; 56: 302-316.
11. Marshall MF, E. Trump, D. Cutaneous involvement in malignant histiocytosis. Case report and review of the literature. *Archives of Dermatology*. 1981; 117: 278-281.
12. Soria C, Orradre JL, Garcia-Almagro D, Martinez B, Algara P, Piris MA. True histiocytic lymphoma (monocytic sarcoma). *Am J Dermatopathol*. 1992; 14: 511-517.
13. Chain MD-C, I. Carbia, S. Xifra, M. Wright, D. Glorio, R. Deves, A. Woscoff, A. Cutaneous true histiocytic malignancy: True histiocytic lymphoma. *Journal of American Academy of Dermatology*. 2004; 50: 9-10.
14. Arai E, Su WP, Roche PC, Li CY. Cutaneous histiocytic malignancy. Immunohistochemical re-examination of cases previously diagnosed as cutaneous "histiocytic lymphoma" and "malignant histiocytosis". *J Cutan Pathol*. 1993; 20: 115-120.
15. Dodd HJ, Stansfeld AG, Chambers TJ. Cutaneous malignant histiocytosis - a clinicopathological review of five cases. *Br J Dermatol*. 1985; 113: 455-461.
16. Dietmar S. Malignant Histiocytosis. *Current Opinion in Hematology*. 2001; 8: 1-4.

17. Sato T, Terui T, Kogawa K, Nagaoka Y, Sato Y, Iyama S, Takada K, Hagiwara S, Takahashi S, Oku T, Matsunaga T, Takahashi M, Kato J, Sakamaki S, Torigoe T, Sato N, Hirayama M, Niitsu Y. A case of true malignant histiocytosis: identification of histiocytic origin with use of immunohistochemical and immunocytogenetic methods. *Ann Hematol.* 2002; 81: 285-288.

18. Mongkonsritragoon W, Li CY, Phyliky RL. True malignant histiocytosis. *Mayo Clin Proc.* 1998; 73: 520-528.

19. Risdall RJ, Dehner LP, Duray P, Kobrinsky N, Robison L, Nesbit ME Jr. Histiocytosis X (Langerhans cell histiocytosis). Prognostic role of histopathology. *Archives of Pathological Laboratory Medicine.* 1983; 107: 59-63.

20. Hsu SM, Ho YS, Hsu PL. Lymphomas of true histiocytic origin. Expression of different phenotypes in so-called true histiocytic lymphoma and malignant histiocytosis. *Am J Pathol.* 1991; 138: 1389-1404.