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HISTIOCYTOSIS X

III. Clinical value of serial biopsies

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The possible development of disseminated histiocytosis from localised eosinophilic granuloma has been discussed for more than 30 years and morphologic transitions have been stated by ENGELBRETH-HOLM et coll. (1944) and AVIOLI et coll. (1963).

It has furthermore been shown that the microscopic appearance of histiocytosis X may be of prognostic significance (NEWTON & HAMOUDI 1973, FREDERIKSEN & THOMMESEN 1978). Only seldom have long-term serial biopsies been reported (SCHAJOWICZ & SLULLITEL 1973). It is not known whether changes in the clinical condition are accompanied by microscopic changes in serial biopsies (LAHEY 1975).

In a clinical material comprising 45 patients with histiocytosis X, serial biopsies were performed in 8. The present report will consider the microscopic appearances of these specimens.

Material and Method

The 8 patients from the period 1945–1975 had a prolonged or divergent clinical course and 2 or more biopsies were performed with specimens available for re-evaluation. When necessary, new sections were made. The specimens were classified as either proliferative, granulomatous, xanthomatous or fibrous type of histiocytosis (ENGELBRETH-HOLM et coll., LEVER 1961).

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Table

Microscopic appearance in serial biopsies of 8 patients with histiocytosis X

Case No.	Age (years)	Sex	Site of lesion and microscopic appearance					
			Biopsy 1	Biopsy 2	Biopsy 3	Biopsy 4	Biopsy 5	Time interval initial—latest biopsy
1	2	M	Osseous granulomatous	Cutaneous unchanged	Mucosal xanthomatous	Mucosal unchanged		3½ years
2	3	M	Lymphnode proliferative	Lymph node unchanged	Cutaneous unchanged	Cutaneous fibrous		3 years
3	3	F	Osseous proliferative	Mucosal unchanged	Cutaneous unchanged	Mucosal unchanged	Cutaneous unchanged	3 years
4	32	F	Osseous proliferative	Cutaneous unchanged	Osseous unchanged	Mucosal unchanged	Cutaneous unchanged	2½ years
5	2	F	Mucosal proliferative	Osseous unchanged	Osseous unchanged			2 years
6	20	F	Mucosal proliferative	Mucosal unchanged	Lymph node normal	Lymph node Hodgkin	Spleen Hodgkin	1½ years
7	57	F	Osseous fibrous	Osseous unchanged	Lung sarcoma	Cutaneous sarcoma		9 months
8	4½	F	Cutaneous proliferative	Subcutaneous sarcoma				1½ years

Results

The age at initial biopsy, the sex distribution, and the sites and number of biopsies and their time intervals are given in the Table.

In cases 1 and 2 a development towards a xanthomatous or fibrous lesion was found, whereas in cases 3, 4 and 5 no changes in the microscopic appearance were apparent. Malignant lesions were observed in the latest biopsies from cases 6, 7 and 8, and these cases are now reported.

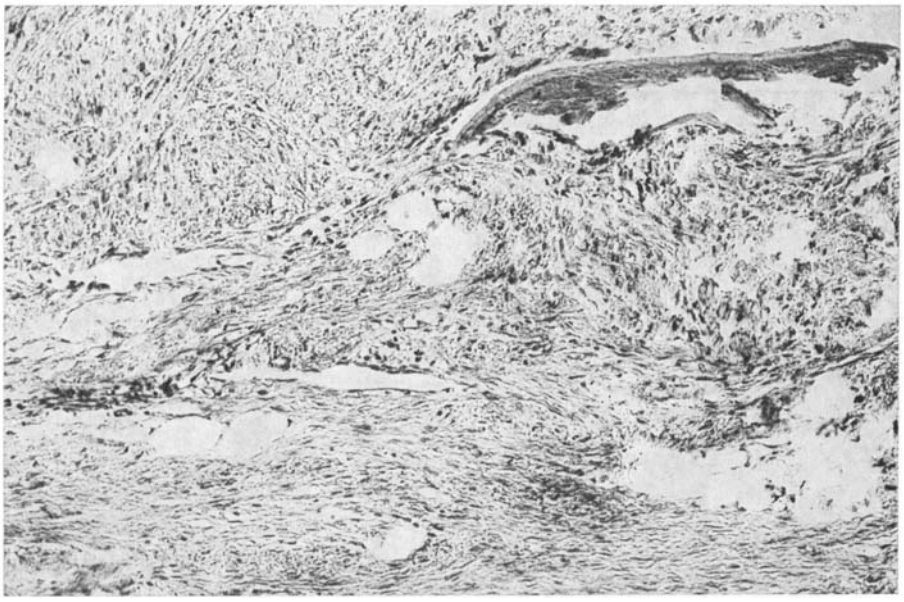


Fig. 1. Case 7. Biopsy from an expanding and lytic bone lesion in the right humeral head and neck. Fibrous tissue compatible with fibrous phase or healing of histiocytosis X. Hematoxylin-Eosin. × 120.

Case 6. The initial lesions were confined to the gingival mucosa and the mandible with loosening of the teeth. Microscopy showed proliferative histiocytosis X composed of benign histiocytes, eosinophils and lymphocytes. Repeated mucosal biopsy 6 months later showed identical findings. Due to pulmonary infiltrations, mediastinal lymph nodes were biopsied, but no abnormalities were found. After radiation therapy (20 Gy) the patient was symptom-free for 1 year. Then swelling of cervical lymph nodes was observed, and subsequent neck node biopsy revealed Hodgkin's disease. The lymphoid tissue was replaced by an intermingling of eosinophils, lymphocytes and atypical histiocytes, some of these of Reed-Sternberg type with huge eosinophilic nucleoli. At staging laparotomy, nodular Hodgkin infiltrates were found in the spleen. A lethal outcome resulted within one year. At autopsy nodular tumour infiltrates in the liver, lymph nodes and bone marrow were found. The primary gingival lesion was fibrosed without microscopic evidence of tumour.

Case 7. On admission to hospital multiple bone lesions were observed in the spine, pelvis, femur and humerus. Particularly a lesion in the right humerus suggested malignancy. Several biopsies only revealed fibrosed stage of histiocytosis X. Radiation therapy relieved symptoms for 3 months; subsequently progression occurred, with cutaneous and pulmonary lesions, where biopsies now suggested malignant histiocytosis. Lethal outcome occurred within 10 months. Autopsy was not performed.

Case 8. This patient had the Letterer-Siwe syndrome diagnosed at 2 years of age. At clinical examination cutaneous elements resembling seborrheic dermatitis and enlargement of the liver and spleen were found. Radiography revealed typical lesions in the skull and the right femur. Biopsies from the liver and a cutaneous element were compatible with histiocytosis X. Remission occurred after treatment with chemotherapeutica. Subsequently

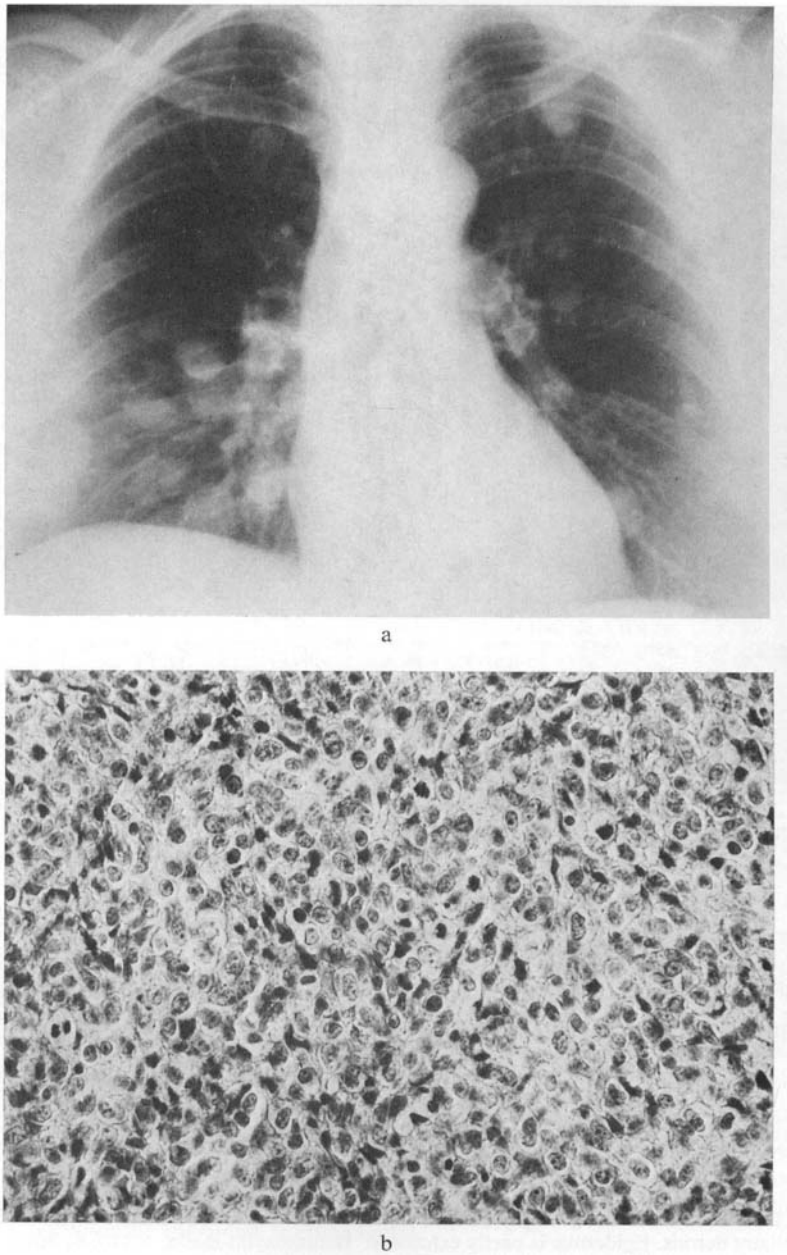
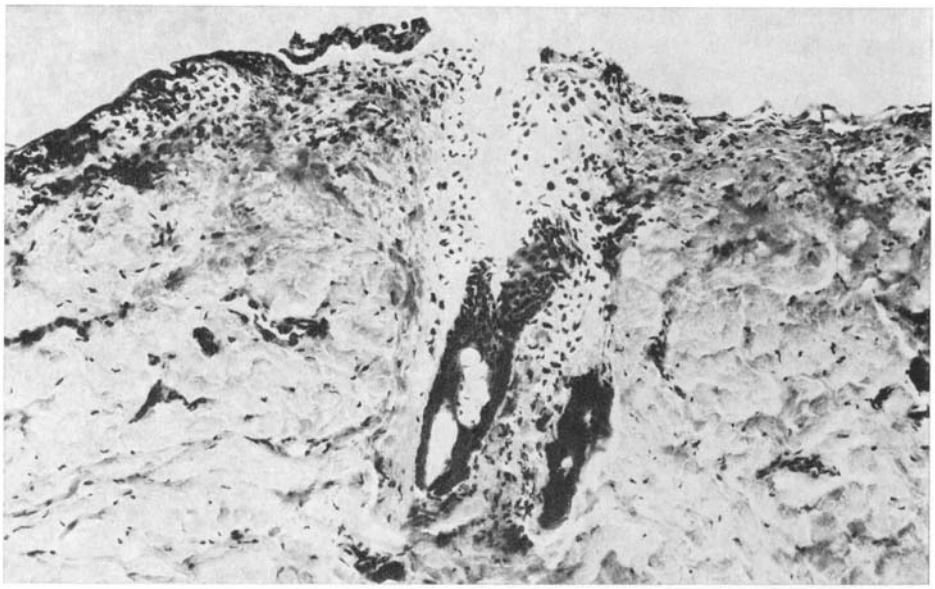


Fig. 2. Same case as Fig. 1. a) Multiple nodular pulmonary infiltrates 6 months later than the biopsy shown in Fig. 1. Sarcomatous cells were present in the fine needle aspirate. b) Surgical biopsy from cutaneous and subcutaneous tumour 2 months later. Closely packed histiocytes, some with atypical nuclear features and some in mitosis. Hematoxylin-Eosin. × 300.



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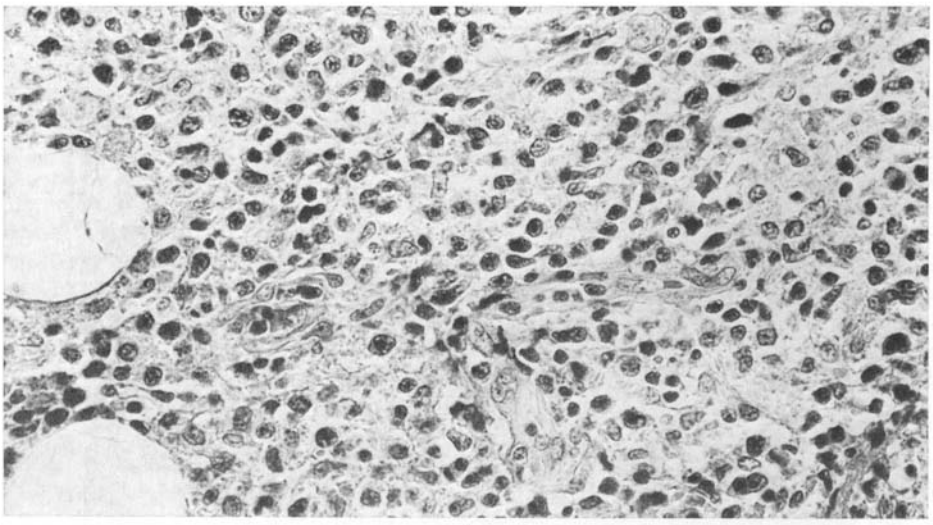

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Fig. 3. Case 8. a) Cutaneous biopsy of lytic lesion in the frontal bone. Histiocytic infiltrate in the papillary dermis. Epidermis is partly exfoliated. Hematoxylin-Eosin. ×120. b) Subcutaneous tumour removed from the posterior aspect of left knee 1½ years later. Malignant tumour cells with highly atypical nuclei, some of histiocytic appearance. Necroses and hemorrhages prevailed in other sections. Hematoxylin-Eosin. ×300.

a subcutaneous tumour, about 4 cm in diameter, was removed from the posterior surface of the left knee. Microscopy then indicated malignant histiocytosis. Two years later additional osseous lesions appeared in the skull. The patient is alive with active disease 5 years after onset of the first symptoms.

Discussion

In this selected series of serial biopsies 2 patients demonstrated a development of the morphologic appearance from initial proliferative lesion to late xanthomatous or fibrous lesion of histiocytosis X as suggested by ENGELBRETH-HOLM et coll. and AVIOLI et coll.

In 3 other cases the microscopic appearance was unchanged, which may be due to an insufficient observation period. The most remarkable finding was that the disease in 3 cases (6, 7 and 8) took a malignant clinical course, repeated biopsies revealing malignant lesions, viz. malignant histiocytosis and Hodgkin's disease.

The distinction based on clinical and microscopic findings between Hodgkin's disease and malignant histiocytosis usually poses no difficulty (RAPPAPORT 1966, BYRNE & RAPPAPORT 1973, WARNKE et coll. 1975). However, both diseases are characterized by a proliferation of neoplastic histiocytes. A wider designation of the histiocytic disorders has recently been proposed by CLINE & GOLDE (1973). In their opinion the histiocytoses are considered to represent a wide spectrum of diseases ranging from well differentiated histiocytoses (unifocal and multifocal eosinophilic granuloma of bone and Hand-Schüller-Christian disease) to poorly differentiated histiocytic disorders such as malignant histiocytosis, reticulum cell sarcoma and monocytic leukemia.

This concept may be supported by the present findings of morphologic transitions in the histiocytoses, both between the various benign histiocytic lesions and particularly by the occurrence of malignant foci.

Repeated biopsies in patients diagnosed as having histiocytosis X may therefore prove valuable, especially in patients with a long clinical course, when aggravation of the clinical condition occurs or when new foci appear.

SUMMARY

In a retrospective review of sequential biopsies in 8 cases of histiocytosis X, 2 developed xanthomatous or fibrous lesions, 3 remained unchanged, whereas 3 developed malignant disease, one Hodgkin's disease and 2 malignant histiocytosis. A possible progression from benign, well differentiated to malignant histiocytic lesion is discussed, and the importance of achieving a microscopic diagnosis is emphasized.

ZUSAMMENFASSUNG

Bei einer retrospektiven Untersuchung von Serien-Biopsien in 8 Fällen von Histiozytosis X, entwickelte sich bei 2 xanthomatöse oder fibröse Veränderungen, 3 verblieben unverändert, während sich bei 3 eine maligne Erkrankung entwickelte, in einem Fall eine Hodgkin-

sche Erkrankung und in 2 eine maligne Histiozytosis. Ein möglicher Fortschritt von einer benignen, gut differenzierten zu einer malignen histiozytären Veränderung wird diskutiert und die Bedeutung, eine mikroskopische Diagnose zu erhalten, hervorgehoben.

RÉSUMÉ

Une étude rétrospective de biopsies séquentielles dans 8 cas d'histiocytose X a montré l'apparition de lésions fibreuses ou xanthomateuses dans 2 cas, le diagnostic est resté inchangé dans 3 cas alors que 3 cas ont présenté une maladie maligne, un cas de maladie de Hodgkin et 2 histiocytoses malignes. Les auteurs examinent la possibilité d'une progression allant d'une lésion histiocytique bénigne bien différenciée à une lésion maligne et ils insistent sur l'importance de faire un diagnostic microscopique.

REFERENCES

AVIOLI L. V., LASERSOHN J. T. and LOPRESTI J. M.: Histiocytosis X (Schüller-Christian Disease): A clinico-pathological survey. Review of ten patients and the results of prednisone therapy. Medicine 42 (1963), 119.

BYRNE JR G. E. and RAPPAPORT H.: Malignant histiocytosis. Gann 15 (1973), 145.

CLINE M. J. and GOLDE D. W.: A review and reevaluation of the histiocytic disorders. Amer. J. Med. 55 (1973), 49.

ENGELBRETH-HOLM J., TEILUM G. and CHRISTENSEN E.: Eosinophil granuloma of bone—Schüller-Christian's disease. Acta med. scand. 118 (1944), 292.

ENRIQUES P., HARRISON E., HAYLES A. B. and BAGGENSTOSS A. H.: Histiocytosis X. A necropsy study of 6 cases. *In:* Second international tutorial on neoplastic hematopathology. Edited by H. Rappaport. Geneva, Switzerland 1976.

FREDERIKSEN P. and THOMMESEN P.: Histiocytosis X. II. Histologic appearance correlated to prognosis and extent of disease. Acta radiol. Oncology 17 (1978), 10.

LAHEY M. E.: Histiocytosis X. An analysis of prognostic factors. Pediatrics 87 (1975), 184.

LEVER W. F.: Histopathology of the skin. Third Edition, p. 326. J. B. Lippincott Company, Philadelphia 1961.

NEWTON W. A. and HAMOUDI A. B.: Histiocytosis. A histologic classification with clinical correlation. *In:* Perspectives in pediatric pathology. Vol. 1, p. 251. Edited by H. S. Rosenberg and R. P. Bolande. Year Book Medical Publishers, Chicago 1973.

RAPPAPORT H.: Tumors of the hematopoietic system. Section III, Fasc. 8, p. 51. Armed Forces Institute of Pathology, Washington 1973.

SCHAJOWICZ F. and SLULLITEL J.: Eosinophilic granuloma of bone and its relationship to Hand-Schüller-Christian and Letterer-Siwe syndromes. J. Bone Jt Surg. 55 B (1973), 545.

WARNKE R. A., KIM H. and DORFMAN R. F.: Malignant histiocytosis (histiocytic medullary reticulosis). Cancer 35 (1975), 215.