DERMATOPATHIC LYMPHADENITIS[1]

Focal Granulomatous Lymphadenitis Associated with Chronic Generalized Skin Disorders

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In the course of a study of a large series of lymph nodes, the concurrence of an unusual focal granulomatous change in the enlarged superficial node and a variety of skin disorders of long duration was noted. The association of chronic generalized skin affections, such as dermatitis exfoliativa, neurodermatitis, parapsoriasis, and eczema, with a generalized superficial adenopathy, led the clinicians in many instances to submit an excised lymph node for histologic examination. It was frequently suspected on clinical grounds either that the skin disease might represent a cutaneous manifestation of an intrinsic disease of the lymph nodes or reticulo-endothelial system, that an early stage of mycosis fungoides in the pre-tumor phase was actually present, or that the patient was suffering from a skin disorder and an independent process such as Hodgkin's disease or lymphosarcoma.

A review of all of the lymph nodes received by the pathology laboratory over a 10 year period revealed that the lesion to be described was associated uniformly with non-specific skin disorders such as those already mentioned. The objectivity of this study is reflected by the fact that in some instances observation of the histologic changes first aroused suspicion that a given node belonged to the "Skin Group," an impression that was verified by the clinical data in every case. On the other hand, because of the variety and non-specific nature of the underlying skin diseases, it was thought that these particular lymph node changes could not be expected to be confined to this group of conditions; however this impression was incorrect, as in every case the correlation was present. The superficial resemblance of this focal granulomatous lesion to changes seen in Hodgkin's disease might lead to an equivocal diagnosis. In this laboratory it has always been felt that the histologic picture should unequivocably not be diagnosed as one of the intrinsic lymph node diseases. The reactive benign nature of the process can be identified histologically, and the diagnosis has been substantiated by the subsequent course of the patient, as disclosed by prolonged follow-up observation. In some cases actual disappearance of the adenopathy has been observed.

Because the association of such lymphadenopathy with skin lesions can arouse the suspicion of a malignant process clinically, and because the benign nature of the histologic change may not generally be appreciated, the following group of cases is reported.

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CLINICAL DATA

This group of twelve patients presents a common clinical background of widespread skin disease of relatively long duration and generalized superficial lymphadenopathy. In only one case (table 1: # 4) generalized adenopathy was not present, the node showing the lesion was removed incidentally during excision of a breast fibroadenoma, and it was only after our interest had been stimulated by the histology that we learned of the presence of a chronic dermatitis. The non-specific nature of the cutaneous lesion is manifested by the variety of dermatologic diagnoses presented, including three cases of neurodermatitis, two cases each of eczema, exfoliative dermatitis, and parakeratosis, and cases of pemphigus foliaceous and atrophia senilis. In every case the adenopathy was so impressive as to arouse clinical suspicion of a possible malignant process.

These cases are all males, ranging from 36 to 78 years of age. Eosinophilia in the peripheral blood was an almost constant feature, at times as much as 35%. Gross hepatosplenomegaly was not present, although the tip of the spleen could be palpated in two instances. The duration of the skin disorder prior to lymph node biopsy varied from six months to more than six years, and follow-up observations up to four and one-half years were recorded. In some cases biopsies had been performed at other institutions and reported by the pathologist as suggestive of a progressive process; review of these slides revealed that the lesion belonged to the category under consideration. An autopsy was performed in one case (table 1: # 1) at another institution, the man dying of pneumonia; there was no evidence of any intrinsic lymph node disease.

The clinical data are summarized in table 1.

MICROSCOPIC DESCRIPTION

A complete transverse section of the enlarged lymph node reveals that the basic architecture is not destroyed. Even in nodes in which the greater portion of the lymphatic tissue is replaced, areas can be found with ease in which the characteristic lymph node structure is fully retained. Cortical follicles are still present, and they include relatively large secondary follicles. The marginal sinus can be followed quite easily, and it shows no unusual conditions. Within the central portion of the lymph node cords of lymphatic tissue are still retained, and they may also include secondary follicles. The intermediary sinuses, however, are difficult to recognize. Whenever one sees them they are wide and filled with reticulum cells.

The most conspicuous feature of the histologic alteration is the presence of areas which stand out from the surrounding lymphatic tissue by their pale appearance. They tend to be situated at the periphery of the node, and are immediately apparent under low power. On closer inspection these islands are composed of accumulations of large polygonal, occasionally stellate cells with an abundant cytoplasm which is often vacuolated. The nuclei are pleomorphous, round, oval, elongated, often kidney-shaped, and are relatively poor in chromatin; the latter is arranged in a fine network, and occasionally in coarser bars. A number of cells contain one or two eosinophilic nucleoli. Because of

TABLE 1

PATIENT	AGE	CLINICAL DIAGNOSES	ADENOPATHY	SPLENOMEGALY	EOSINOPHILIA	DURATION OF SKIN DISEASE BEFORE BIOPSY	DURATION OF FOLLOW-UP	COMMENTS
					%			
1. F. Z.	51	Exfoliative dermatitis, lymphosarcoma	+	0	?	1½ years	2 months	Died. Autopsy: lobular pneumonia; no intrinsic lymph node disease
2. M. S.	71	Mycosis fungoides	+	0	16	6 months	2 years	Biopsy, 5 months later, another hospital, reported "mycosis fungoides in pretumor phase"
3. J. H.	36	Parakeratosis, mycosis fungoides	+	0	35	6 months	10 months	Moved out of state
4. H. L.	36	Pemphigus foliaceous	0	0	13	3 years	0	Previous biopsy at another hospital, reported "inconclusive"
5. L. T.	38	Parakeratosis, Hodgkin's disease	+	0	29	11 months	4½ years	Marked decrease in adenopathy
6. A. R.	75	Neurodermatitis, Hodgkin's disease	+	0	12	3 years +	3 years	
7. H. F.	54	Neurodermatitis, follicular lymphoblastoma	+	Tip	38	6 months	2½ years	Disappearance of nodes and skin lesions
8. E. N.	47	Exfoliative dermatitis	+	0	24	6 months	2 years	Clinical improvement
9. H. R.	78	Eczema, metastatic malignancy	+	0	17	6 years +	3 years	2 biopsies, 11 months apart, showed "skin" change. Died at home, heart disease
10. H. T.	50	Neurodermatitis, Hodgkin's disease	+	0	7	3 years	3 years	2 previous admissions without skin or node disease. 3 biopsies in 3 years, showing evolution of lesion
11. H. R.	71	Atrophia senilis, Hodgkin's disease	+	1 cm.	20	2 years	6 months	Previous biopsy, at another hospital, reported "suspicious of leukemia"
12. L. R.	39	Eczema, mycosis fungoides	+	0	8	1½ years	4 months	Still under observation

the prominence of these cells, the islands which replace the lymphatic tissue appear much paler than the substituted tissue. Mingled with these cells, which can be identified with histiocytes, there are cells of the same appearance containing golden brown pigment granules which on special stain can be identified as iron pigment. In addition the definite presence of melanin pigment can be demonstrated by the bleaching test and the reduction of silver salts. The relative predominance of melanin and iron varies from case to case, the pigment in a

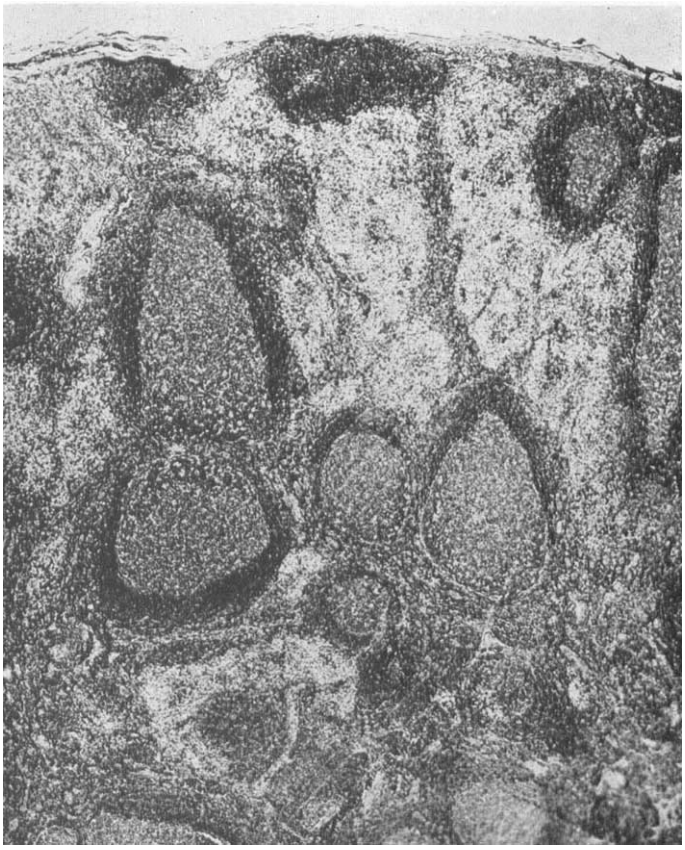

FIG. 1. The pale area of replaced lymphatic tissue stands out clearly from the adjacent tissue in which the lymph node architecture is preserved (× 15).

given node consisting of melanin or iron or both. Within the meshes of this fundamentally cellular and fibrillar reticulum there are numerous eosinophilic leucocytes, polymorphonuclear leucocytes, plasma cells, and large and small lymphocytes (figs. 1 and 2).

The delineation of these areas from the lymphatic tissue is not always sharp, and at the border lymphocytes from the preexisting lymphatic tissue mingle with the adjacent histiocytes and vice versa. The lymphatic tissue nests show a considerable number of plasma cells and occasional eosinophilic leucocytes.

The infiltration of the lymphatic cords with plasma cells may be so extensive that the lymphocytes are completely replaced. Mitotic figures can be found quite frequently within the large lymphocytes.

The secondary follicles of the remaining lymphatic tissue are formed by large polygonal cells with very pale, often actually vesicular nuclei, showing only occasionally a nucleolus, and quite abundant cytoplasm. These cells can be identified as histiocytes, while the greater number of the other cells show a nucleus richer in chromatin. The latter cells are diagnosed as lymphocytes or lymphoblasts, and frequently show mitotic figures. The ratio of histiocytic reticulum cells to lymphoblasts in the secondary follicles varies considerably. Because of the association of lymphoblasts with reticulum cells, the secondary

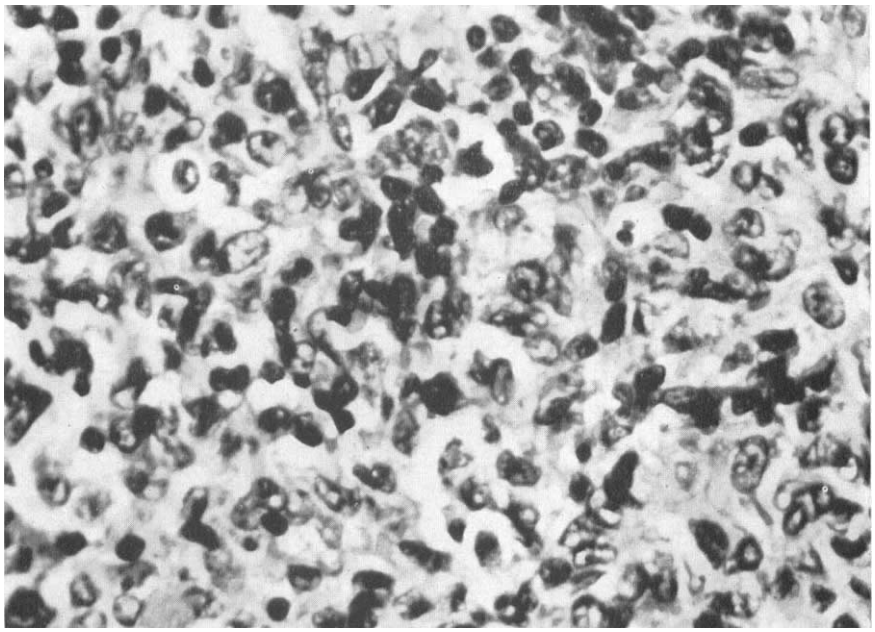

FIG. 2. The predominant cells of the pale area are large reticulocytes, many with histiocytic differentiation containing pigment and lipoid deposits (× 630).

follicles can be differentiated from the nests of reticulum cell proliferation which constitute the major portion of the affected node.

The widely dispersed areas of reticulum cell proliferation show moderate vascularization, which is more conspicuous within the secondary follicles and the adjacent lymphatic tissue. The post-capillary veins with prominent endothelial cells are seen within the expanded reticulum cell islands, and occasionally show hyalinization of the wall. Between the cellular elements of the islands there is expanded a fine network of fibrillar reticulum, which in silver stains is very conspicuous; in some regions the fibers are quite thick.

The most striking characteristic of these nodes, therefore, is the patchy, alopecia-like replacement of the lymphatic tissue by pleomorphous aggregates

of cells, among which reticulum cells with histiocytic differentiation are most prominent. The association of these cells with eosinophilic leucocytes as well as with plasma cells and occasional fibroblasts may simulate the histologic picture of Hodgkin's disease, although the specific elements, such as the characteristic giant cells with the conspicuous nucleoli are always absent. Inasmuch as the ratio between retained lymphatic tissue and the reticulum cell areas may vary, confusion may also arise with the picture of follicular lymphoblastoma. For the experienced eye, however, this diagnosis can be ruled out immediately, because the constituent cells of the reticulum cell proliferation reveal definite phagocytic activity, which is absent in the real instances of follicular lymphoblastoma.

From the histologic description it is evident that the alteration is fundamentally due to reactive proliferation of the reticulum cells, and the inflammatory character of the morbid process is further evidenced by the presence of eosinophilic leucocytes and plasma cells. Such extensive reticulum cell proliferation, however, is very unusual, and has been seen infrequently in a series of several hundred lymph nodes, among which chronic lymphadenitis was most common.

DISCUSSION

Pautrier and Woringer, in 1932 and 1937, described a series of cases similar to those under consideration, with striking lymphadenopathy associated with skin disorders (8, 9). From their microscopic descriptions and pictures, it is apparent that they were dealing with the same lesion that we are presenting here. There was the same initial potential clinical and histological confusion with a malignant process. Their group included eleven cases, both females and males, with varying types of dermatoses, and a uniform microscopic picture in the excised lymph node. They recognized the benign nature of the lymphadenopathy, for which they coined the term "lipo-melanotic reticulosis." The presence of melanin in the lymph nodes was ascribed to increased absorption and lymphatic transportation from the skin. "Lipo-melanotic reticulosis" was subsequently reported by Pinetti (10) in cases of erythrodermia and psoriasis, by Goedhart (5) in a case of exfoliative dermatitis, and by Soloff in a boy of 17 with a chronic inguinal pruritus (11).

Midana (7) studied the lymph node changes in thirteen cases of chronic dermatoses, and described changes similar to those above. His pictures, however, show a generalized cellular hyperplasia, rather than the localized areas under present consideration. Another suggestive case was described by Duany (4) in a two-year old infant, with a two year follow-up. Cannon (2) collected a group of patients with allergic dermatitis in whom the adenopathy was so striking as to suggest a clinical diagnosis of lymphoblastoma. The subsequent clinical courses showed this impression to be incorrect. Histologic studies of lymph nodes were made in only two cases, and were reported as chronic inflammation.

The conclusions of all of these authors have essentially been in agreement with our findings, namely that the adenopathy was of a benign, reactive nature in response to the skin diseases as an irritant. On the other hand, the report

of Combes and Bluefarb (3) stresses possible malignant sequelae. Their microscopic studies of lymph nodes in fifteen cases of skin disorders associated with generalized lymphadenopathy led them to interpret the changes as "giant follicular lymphadenopathy." This they consider to be a condition which is radio-sensitive, and which may either regress or undergo transformation into sarcoma. Because of the present state of confusion in the literature regarding "follicular lymphoblastoma" and "giant follicular lymphadenopathy," these findings are somewhat difficult to interpret. We have already indicated that the follicular hyperplasia in the lymph nodes associated with dermatoses differs definitively from that in follicular lymphoblastoma. The essential histologic features differentiating follicular lymphoblastoma from the simple follicular hyperplasia accompanying a hyperplastic lymphadenitis are under investigation at present.

Mention must also be made of a report on the relation of lymph nodes to skin diseases by de Amicis (1) in the German literature, which we have been unable to obtain due to war conditions.

Although it is apparent that Pautrier and Woringer recognized that they were dealing with a benign process, and that the lymph node changes were due to the skin disease, it is felt that the term "lipo-melanotic reticulosis" is both inaccurate and misleading. Although many of the histiocytes are lipophages, and melanin pigment is present, these are not representative of the constant, outstanding, or essential features of the process. In addition, contrary to all of the reports above, the presence of iron as well as melanin pigment was demonstrated in many of the cases in the present series. This is in keeping with the findings of Jadassohn, who noted melanin in a case of pityriasis rubra, and iron pigment in the cutis and regional lymph nodes in two cases of eczema (6). The variable amounts of the two pigments in these nodes may be a function of the type of dermatitis as well as the degree of pruritus. The pigment migration is part of the irritative process which causes the granulomatosis, and supports fully the contention that the lymphadenopathy is dependent on the skin disease. It is this granulomatous replacement of the lymphatic tissue, with reticulum cell proliferation and histiocytic transformation as well as fibroblastic differentiation that constitutes the characteristic feature of this condition.

The recognition of the histologic picture, which is quite characteristic and striking, is of importance to avoid errors in diagnosis which might occur because of a somewhat superficial similarity to Hodgkin's disease, and because the striking follicular hyperplasia might also lead to an erroneous impression.

SUMMARY

1. Attention is called to the occurrence of generalized lymphadenopathy in association with a variety of chronic skin disorders characterized by pruritus.

2. Clinically the majority of the cases here reported were suspected to be instances either of an intrinsic lymph node disease, such as Hodgkin's disease or lymphosarcoma with cutaneous involvement, or of mycosis fungoides with secondary lymph node infiltrations.

3. The granulomatous character of the morbid process of the lymph node might lead to confusion with Hodgkin's disease; however the histologic features when properly analyzed unequivocably point to a benign, reactive process.

4. The absence of a progressive lymph node disease has been substantiated by prolonged follow-up observation.

5. Identical lesions have been reported by Pautrier and Woringer under the name of "lipo-melanotic reticulosis." It is felt that this term is not sufficiently comprehensive, since it fails to emphasize both the outstanding features of the condition, and the fact that the lymphadenopathy is dependent on the skin disease.

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