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Mast Cell Changes in Skin Diseases

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Mast cell changes, numbers and degranulations, of 264 cases of skin biopsy lesions were studied. An increase of mast cells was noted in congenital diseases; non-infectious erythematous, papullar, and squamous diseases; vascular diseases; bacterial diseases; fungal diseases; lipidoses; metabolic diseases; connective tissue diseases; tumors and cysts of the epidermis; tumors of epidermal appendages; tumors of fibrous tissue; tumors of vascular tissue; and benign tumors of melanocytes. The increase was noted mainly in the surrounding areas of the lesions rather than within the lesions. In only a few conditions; vascular diseases, connective tissue diseases, and tumors of vascular tissue, an increase of mast cells within the lesion was noted. With regard to the relation between mast cell changes and gross appearance of skin lesions, an increase of mast cells was observed in the surrounding areas of scally, vesicular, nodular or warty, and ulcerated lesions. Relationship between the degree of degranulation to the types of skin disease or gross appearance can not be clearly established. In all conditions, the increase of mast cells was intimately associated with formation of new fibrous connective tissue.

Mast cells vary in numbers from species to species, and within a given species there is a variation from organ to organ. They are particularly numerous in organs and structures rich in connective tissue, such as mammary glands, tongue, prostate, lungs, and omentum, as well as in the various layers of the gastrointestinal tract, in serous membranes, and in the skin.

Mast cells vary in size by species, but they are generally large and contain numerous granules which stain with metachromatic dye. Chemically, mast cell granules contain three major substances, heparin (Holmgren and Wilander, 1937; Jorps *et al.*, 1937; Riley and West, 1953), histamine (Fawcett, 1955) and serotonin (Hagen *et al.*, 1959; Benditt *et al.*, 1955; Lagunoff *et al.*, 1964). In addition to these, mast cell granules have been reported to contain dopamine, protease, phosphatidase A, glucuronidase, acid and alkaline phosphatase, ATPase. Other enzymes, such as dopa decarboxylase, histidine decarboxylase, 5-hydrotryptophan decarboxylase, and heparin-forming enzymes, are believed to be in the nonparticulate fraction of the mast cell (Uvnas, 1964).

Mechanical, chemical and physical injury can

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cause degranulation of mast cells and release of substances contained in the granules (Uvnas, 1964). Among chemical agents are polymer substance, monomer basic substances, and surface-acting agents. Janoff *et al.* (1965) demonstrated that basic protein in leukocyte lysosomes also degranulates mast cells. The physical agents which degranulate mast cells are heat, ultraviolet radiation, X-ray and radioactive isotopes (Uvnas,1964).

In addition to these, antigen-antibody interaction in or on the mast cell brings about degranulation (Austen and Bloch, 1965), in two forms; a cytotoxic injury requiring all complements, a mechanism identical to the lysis of red cells by antibody and complement; and anaphylactic injury requiring a specific anaphylactic or mast-cell sensitizing antibody (Mota, 1964).

The physiologic role of mast cells is known very little, but their characteristic perivascular distribution suggest that the agents released from mast cells regulate the blood flow through the terminal vascular bed. Under abnormal conditions amines may be released excessively from mast cells and cause severe manifestations. Systemic anaphylaxis of the guinea pig and dog is mediated by histamine released from mast cells. In anaphylaxis of the rat both histamine and serotonin play a significant role (Mota, 1964). Histamine and serotonin released during the early phase of inflammatory reaction and responsible for leakage from venules (Spector and Willoughby, 1965) originate probably from mast cells. Therefore, the mast cell, thought not an inflammatory cell in the strict sense, plays an important role in the mediation of the vascular phenomena of the inflammation by releasing histamine and serotonin.

The skin contains considerable numbers of mast cells, and is the site of various physicochemical injuries and inflammatory reactions. Thus it is likely that the mast cells in the skin play an important role in the response of the skin to various conditions, beside the fact that a certain disease of the skin, namely urticaria pigmentosa, the mast cell is the basic component. Therefore, it would be interesting to study mast cell reactions in various skin disorders with correlation of clinical appearance and the types of histopathologic lesions.

MATERIALS AND METHODS

Materials consist of skin biopsies received during 1977 by the Department of Pathology, Yonsei Medical Center from the outpatient clinic. The specimens are processed for routine histopathologic technique, namely fixation in 10% neutral formalin followed by paraffin embedding. Hematoxylin-eosin stained sections were examined for histopathologic diagnosis, and mast cell staining by the method of Dominici was applied to every specimen. The study of mast cells included the numbers of mast cells by location (normal part, within the lesions, and surrounding areas of the lesions) and the degree of degranulation. Then a comparison of the findings of intact skin and those of the disease part was made. The numbers and degranulation of mast cells of the lesions were expressed in relative scores against those of the normal part of the skin which is set as score 1. When they are increased the score is more than 1 and when they are reduced the score is less than 1. Gross appearance of the lesions (erythematous, papullar, patchy, scally, ulcerated, etc.) were checked and compared with mast cell numbers and the degree of degranulation to see if there was any correlation between mast cell response and the gross appearance of the lesion.

RESULTS

A. Types of skin lesions:

A total of 264 cases of skin lesions were examined. The types of skin lesions were divided into disease groups according to the histopathologic features and are summarized in Table 1. The most common groups in the biopsy materials in order of frequency were tumors and cysts of the epidermis; non-infectious erythematous, papullar and squamous diseases; connective tissue diseases; bacterial diseases; congenital diseases; and non-infectious vesicular and bullous diseases. Among tumors and cystic diseases of the epidermis, epidermal cysts were the most common followed by epidermoid carcinomas, solar keratoses and papillomas. Among non-infectious erythematous, papullar, and squamous lesions, psoriasis occupied 70% and the psoriasis was the most common single disease entity among all biopsy specimens. Among bacterial diseases, leprosy was the most common lesion being more than 60%. The congenital diseases showed a relatively even distribution among ichthyosis, epidermolysis bullosa, keratosis palmaris et plantaris, and porokeratosis. Dermatitis was the most common lesion among noninfectious vesicular and bullous diseases, followed by bullous pemphigoid, dermatitis herpetiformis and erythema multiforme. Among connective tissue diseases, lupus erythematosus occupied 50% followed by scleroderma.

Table 1. Types and Frequencies of Skin Lesions by Histopathologic Features

Groups of skin diseases	No. of cases
Congenital diseases	20
Non-infectious vesicular and bullous	18
Non-infectious erythematous, papular, and squamous	31
Vascular	11
Inflammatory diseases of appendages and cartilage	4
Inflammatory diseases due to physical & foreign bodies	4
Non-infectious granulomas	0
Inflammatory diseases of subcutaneous fat tissue	10
Eruptions due to drugs	5
Degenerative diseases	1
Bacterial diseases	23
Treponemal diseases	1
Fungal diseases	10
Protozoal diseases	0
Diseases caused by viruses	7
Lipidoses	4
Metabolic diseases	1
Pigmentary disorders	0
Connective tissue diseases	25
Tumors and cysts of the epidermis	45
Tumors of the epidermal appendages	8
Metastatic carcinoma	1
Tumors of fibrous tissue	8
Tumors of vascular tissue	9
Tumors of fat tissue	1
Tumors of neural tissue	1
Melanocytic nevi and malignant melanoma	14
Lymphoma and leukemia	2
Total	264

B. Numbers of mast cells and degree of degranulation in various skin diseases.

Numbers of mast cells and the degree of degranulation in various types of skin diseases were summarized in Table 2. The numbers of mast cells are examined at three different parts, namely normal part of the skin, within the lesions and the areas surrounding the lesions. The degree of degranulation was examined on the mast cells within and surrounding the areas of the lesions. An increase of mast cells within the lesions was observed in vascular diseases, connective tissue diseases, tumors and cysts of epidermis, and the tumors of vascular tissue.

Table 2. Numbers of Mast Cells and Degree of Degranulation in Various Groups of Skin Diseases

Groups of skin diseases	Number of mast cells N.	L.	S.	Degranulation
Congenital diseases	1.0	0.5	1.6	1.2
Non-infectious vesicular and bullous diseases	1.0	0.4	0.6	0.7
Non-infectious erythematous, papullar, and squamous diseases	1.0	0.6	1.4	1.8
Vascular diseases	1.0	4.8	0.5	0.5
Infectious diseases of skin appendages and cartilages	1.0	1.0	3.0	2.0
Inflammatory diseases due to physical and foreign agents	1.0	0.0	0.4	0.1
Inflammatory diseases of subcutaneous fat tissue	1.0	0.8	1.0	1.0
Eruptions due to drugs	1.0	0.0	0.8	1.0
Degenerative diseases	1.0	0.0	0.0	0.0
Bacterial diseases	1.0	0.8	1.4	0.8
Treponemal diseases	1.0	0.0	0.0	0.0
Fungal diseases	1.0	0.0	1.3	1.0
Diseases caused by viruses	1.0	0.0	0.6	0.7
Lipidoses	1.0	0.0	2.6	2.6
Metabblic diseases	0.0	0.0	3.0	0.0
Connective tissue diseases	1.0	1.3	1.6	0.6
Tumors and cysts of epidermis	1.0	1.3	2.4	2.4
Tumors of epidermal appendages	1.0	0.3	3.8	3.3
Metastatic carcinoma	0.0	0.0	1.0	0.0
Tumors of fibrous tissue	1.0	0.4	2.6	1.2
Tumors of vascular tissue	1.0	1.5	1.2	0.8
Pigmented nevi	1.0	0.4	2.5	1.6
Mycosis fungoides	1.0	1.5	0.0	1.0

N : Normal part of the skin
L : Within the lesions
S : Surrounding areas of the lesions

An increase of mast cells in the surrounding areas of the lesions was observed in congenital diseases; non-infectious erythematous, papular, and squamous diseases; bacterial diseases; fungal diseases; lipidosis; connective tissue diseases; tumor and cysts of epidermis; tumors of epidermal appendages; tumors of fibrous tissue; tumors of vascular tissue and nevi. In general, increase of mast cells was more frequently observed in the surrounding areas than within the lesions. Increase of mast cells within the lesion was noted in allergic vasculitis, hemangioma, seborrhoiec keratosis, epidermal cysts, and solar keratosis, while an increase in the surrounding areas of the lesions was noted in ichthyosis, keratosis palmaris et plantaris, porokeratosis, keratosis follicularis, psoriasis, pityriasis, erythema induratum, chancroid, tinea, xanthoma, nevus sebaceum, dermatofibroma, and pigmented nevi.

Degree of degranulation was increased in the disease group of non-infectious erythematous, papular, and squamous diseases; lipidoses; tumors and cysts of the epidermis; tumors of epidermal appendages; and nevi. Degranulation was increased in erythema multiforme,

Table 3. Numbers of Mast Cells and Degree of Degranulation in Relation to the Gross Appearance of the Skin Lesions

Nature of gross appearance	Numbers of mast cells			Degranulation
	N.	L.	S.	
Erythematous	1.0	0.8	1.0	1.2
Macullar	1.0	0.9	1.1	1.1
Patchy	1.0	0.2	2.0	1.5
Papullar	1.0	0.8	1.0	1.2
Scally and crusted	1.0	0.5	2.7	1.0
Vesicular and bullous	1.0	0.2	2.2	1.0
Nodular and warty	1.0	0.4	2.0	1.0
Pigmented	1.0	0.7	1.4	0.7
Ulcerated	1.0	0.9	2.0	1.3
Scar	1.0	1.0	1.0	0.0

N : Normal part of the skin
L : Within the lesions
S : Surrounding areas of the lesions

seborrhoiec keratosis, solar keratosis, erythroplasia, epidermoid carcinoma, and basal cell carcinoma, and nevus sebaceum.

C. Status of mast cells in relation to the gross clinical appearance of the lesions.

Numbers and degree of degranulation in relation to the gross clinical appearance of the lesion are summarized in Table 3. There was no significant increase of mast cells either in the lesions or the surrounding areas in erythematous, macular, or pigmented lesions. Increase of mast cells in the area surroudning the lesion is noted in patchy, papullar, scally and crusted, nodular or warty and ulcerated lesions. However, no increase of mast cells within the lesions in relation to gross appearance was noted. The degree of degranulation was increased in patchy, papullar, and ulcerated lesions, and slightly increased in erythematous lesions. In the remaining types no increase of degranulation was noted.

DISCUSSIONS

A considerable number of mast cells are present in the dermis of normal skin. They are distributed mainly in the vicinity of capillaries are most abundant (Hashimoto *et al.*, 1967; Okonkwo *et al.*, 1965).

Mikhail and Miller-Milinska (1964) reported that the number of mast cells is increased in many inflammatory conditions where they are intermingled with various inflammatory cells, for instance, in the granulation tissue of healing wounds, and in atopic dermatitis, lichen planus, lupus erythematosus, and pemphigus vulgaris. Cowley and Hoch-Legeti (1961) and Crowe *et al.* (1965) reported that there is a marked increase of mast cells in the stroma of benign tumors of the skin.

In the present study, numbers of mast cells are particularly increased in the surrounding areas of the lesions of congenital diseases; non-infectious erythematosus, papullar and

squamous diseases; bacterial diseases; fungal diseases; connective tissue diseases; lipidoses; tumors and cysts of epidermis; tumors of epidermal appendages; tumors of fibrous tissue; tumors of vascular tissue; and pigmented nevi. However, an increase of mast cells within the lesions was observed in only a few conditions, namely, vascular diseases; especially allergic vasculitis, connective tissue diseases; tumors and cyst of the epidermis; and the tumors of vascular tissue. As a whole, the increase of mast cell was more frequent and marked in the surrounding areas of the lesion than within the lesion itself. An increase of mast cells with vascular tumors was particularly noted in capillary and mixed types of hemangiomas whereas no appreciable increase was found in cavernous hemangiomas.

The increase of mast cells in the surrounding areas of the lesions was associated with either increased vascularity or formation of new fibrous connective tissue. Therefore, it appeared that an increase of mast cells in skin diseases are more closely related with collagen formation. Asboe-Hansen (1973) stated that the mast cells participate in all diseases of connective tissue, and no new formation of connective tissue takes place without a demonstrable activity of mast cells. Rasmussen (1966) and Wichmann (1955) reported that mast cells are scarce in the early stage of granulation tissue in the process of wound healing. Asboe-Hansen (1950) reported an increase of mast cells in keloid. Sheldon and Bauer (1960) demonstrated that fibroblastic proliferation was retarded when mast cell granules were depleted beforehand in experimental cutaneous mucormycosis.

Asboe-Hansen (1950) and others Cramer and Simpson, 1944; Engelbreth-Holm and Asboe-Hansen, 1953; Cawley and Hoch-Legeti, 1961) reported that a great increase of mast cells is noted in the stroma of cutaneous carcinogenesis and benign skin tumors. The moment the tumors grow malignant, the mast cells disappear. Therefore it was suggested that the mast cells and their products play a part of local tissue resistance against the development and growth of the tumors.

An increase of mast cells in various types of connective tissue diseases, particularly in lupus erythematosus and scleroderma, was reported by Asboe-Hansen (1973) and he related this to mucoid degeneration followed by collagenous fibrosis in connective tissue diseases.

Correlation between gross features of the skin lesions and the state of mast cells is not clearly demonstable in the present study. No relation between gross appearance and the numbers of mast cells within the lesion was found. However, an increase of mast cells in the surrounding areas of the lesions was observed in scally, crusted, vesicular, nodular or warty and ulcerated lesions. These lesions were mostly associated with fibrosis. A slight to moderate increase of degranulation was observed in erythematous, papullar and ulcerated lesions. However, the degree of degranulation was not prominent. Asboe-Hansen (1973) stated that mast cells are increased in itching dermatoses, such as, neurodermatitis, atopic dermatitis, lichen planus, nummular eczema, urticaria, dermatitis herpetiformis, and erythema multiforme. No other studies of mast cell changes in relation to gross clinical features of the skin lesions, however, are available. Once again, it is likely that the mast cell variations in relation to the appearance of the lesions is more dependent on the degree of fibrous tissue formation rather the nature of gross features.

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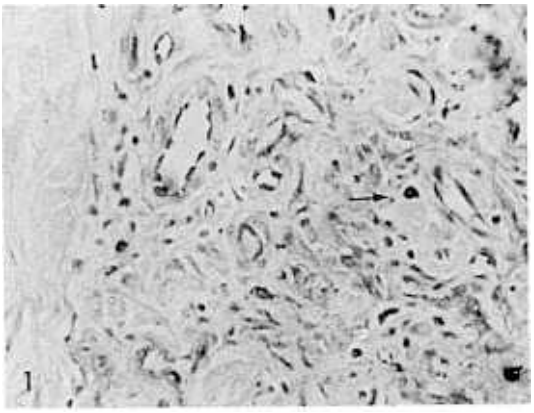

Fig. 1. Slightly increased numbers of mast cells within a mixed type of hemangioma X. 430.

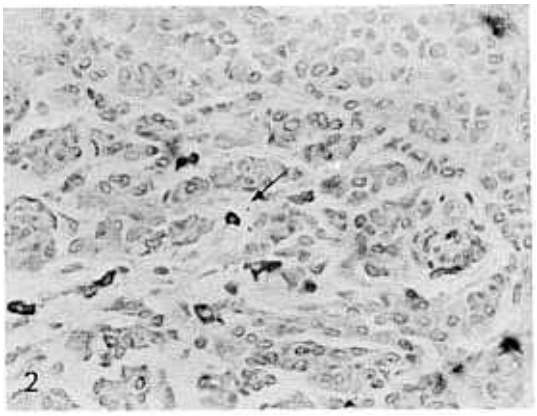

Fig. 2. Moderately increased numbers of mast cells within a seborrheic keratosis X. 430.

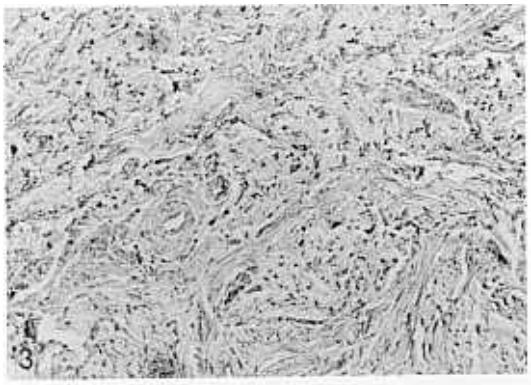

Fig. 3. Marked increase of mast cells in surrounding areas of a fibrous-histiocytoma X. 100.

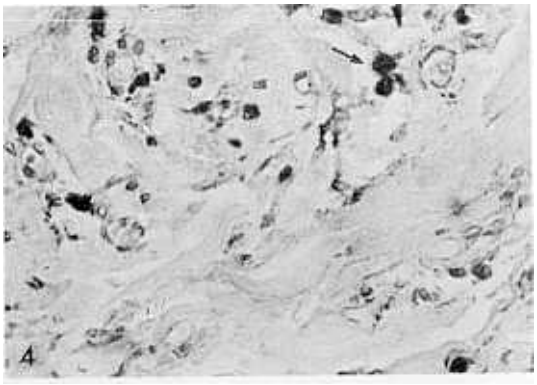

Fig. 4. Higher magnification of a portion of Fig. 3. showing intimate apposition of mast cells with collagen bundles X. 430.

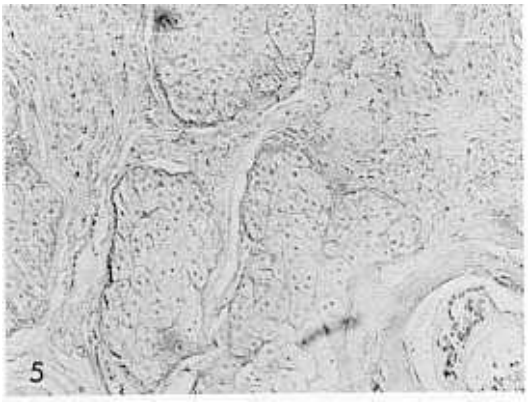

Fig. 5. Marked increase of mast cells in the surrounding stroma of nevus sebaceous X. 100.

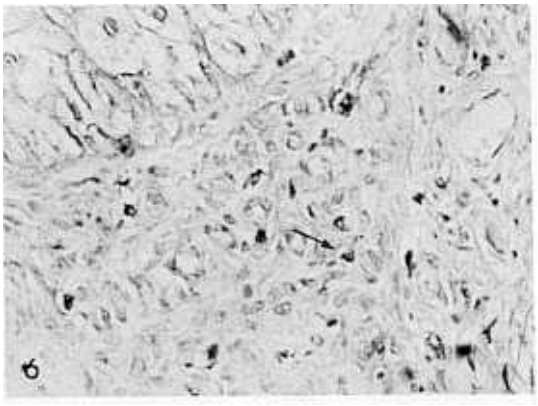

Fig. 6. Higher magnification of a portion of Fig. 5. showing intimate association of mast cells with cepillaries and fibroblasts X. 430.