URTICARIA PIGMENTOSA WITH BONE INVOLVEMENT

Mast Cell Aggregates in Bones and Myelosclerosis Found
At Autopsy in a Case Dying of Monocytic Leukemia*

F. SAGHER, M.D., E. LIBAN, M.D., H. UNGAR, M.D. AND S. SCHORR, M.D.

Following the first recorded observation of bone lesions in a case of urticaria pigmentosa in 1952 (1) a number of reports have appeared in which bone involvement has been described (2—7). The bone lesions noted thus far on X-ray examination have been of two different types: (1) generalized wide-spread osteoporotic and osteosclerotic areas and (2) similar areas confined mainly to the skull, femur or humerus.

The question concerning the nature of these bone lesions remained open. Sternal or rib bone marrow puncture in which large numbers of mast cells were sometimes found suggested that skin and bone lesions are of the same nature (7, 8). The following is a report of a case of urticaria pigmentosa in which bone lesions were followed for two years prior to the patient’s death from monocytic leukemia and in which post-mortem examination was subsequently performed.

REPORT OF CASE

The patient, a woman aged 55, was referred to the Dermatological Outpatient Department in 1953. Her chief complaints were a skin eruption, general malaise and loss of weight amounting to about 10 kg during the preceding five years. The skin eruption had first appeared more than five years earlier, involving the trunk, the upper and lower extremities and especially the forehead and scalp. Itching was very slight and occurred mainly at night. The history revealed that she had had a daily temperature of up to 38°C during the preceding year. The family history was negative for skin and neoplastic disease.

Examination revealed an eruption involving the whole face, the scalp, the trunk and the extremities, diminishing in intensity peripherally. The lesions were discrete, fairly numerous, mostly macular and papular; on the forehead and inner parts of the thighs the lesions were denser than elsewhere. The color of the lesions was brownish-red; they were round or oval in shape, and their diameter varied between 2 and 10 mm. On stroking the skin, a distinct whealing occurred in the lesions which became about two or three times their previous size. The normal skin showed redness but no urtication following irritation.

The patient’s general condition was poor but examination revealed no other specific abnormalities; the lymph nodes were not enlarged; the liver and the spleen were not palpable.

Two biopsy specimens from different parts of the affected skin revealed mast
Fig. 1. A) Skin specimen one month before death. Typical picture of urticaria pigmentosa with metachromatic tissue mast cells scattered in the upper and mid-dermis. Toluidine blue. X125. B) Skin specimen taken at autopsy from an urticaria pigmentosa lesion near the umbilicus. Dense monocytic infiltrations in the whole dermis, with many capillaries filled with monocytic cells. Hematoxylin and eosin. X85.

Fig. 2. Peripheral blood smear, July, 1955. Monocytic cells are seen, containing large, round, oval, indented or lobulated nuclei with coarse chromatin. Many fine azurophilic granules are scattered in the slightly basophilic cytoplasm. May-Gruenwald-Giemsa. X1,500.
cell accumulations in the upper and mid-dermis characteristic of urticaria pigmentosa.

**X-ray examination, July, 1953**

_**Ribs:**_ Sclerosed trabeculae along the entire course of the bones with tiny demineralized areas scattered between these trabeculae.

_**Pelvis, dorsal and lumbar spine:**_ Thickened trabeculae with tiny interspaces throughout the vertebral bodies, pelvis and head and neck of each femur.

_**Skull:**_ Numerous tiny islets of increased density dispersed throughout the whole skull, involving also the diploe; margins of inner and outer tables distinct.

_**Extremities:**_ Trabeculae of spongiosa of the shafts of the long bones thickened and indistinct; outline of cortex normal; bony pattern of distal parts of radius and ulna, the carpal bones, metacarpals and phalanges of each side completely normal.

**Laboratory examinations**

_**Urine:**_ Routine chemical and microscopic examination revealed no abnormal findings.

_**Stool:**_ Microscopic examination revealed no abnormal findings.

_**Blood:**_ Erythrocytes 3,900,000 per cu. mm; Hb. 80 per cent; leukocytes 6,000 per cu. mm with 27 per cent segmented neutrophiles, 2 per cent eosinophiles, 54 per cent lymphocytes and 17 per cent monocytes. Wassermann Reaction and Kahn test negative. Blood phosphorus 3.1 mg%; alkaline phosphatase 5.8 Bodansky units; serum calcium 10.7 mg%.

During the subsequent two years the patient was seen several times; the only changes observed were in the radiological appearances of the bones and these are described below. In June, 1955, however, her general condition began to worsen. Two skin biopsies again showed the typical features of urticaria pigmentosa (Fig. 1, A) and blood examination revealed the following picture: erythrocytes 3,700,000 per cu. mm; leukocytes 43,400 per cu. mm with 8 per cent polymorphonuclear leukocytes, 14 per cent bandforms, 1 per cent eosinophiles, 11 per cent lymphocytes, 50 per cent monocytes and 16 per cent atypical cells of a monocytic type (Fig. 2).

This picture suggested monocytic leukemia and the patient was hospitalized in July, 1955. On admission she was cachectic, her weight being 45 kg. All superficial lymph nodes were enlarged. The liver was palpable and firm, extending about 6–8 cm below the costal margin; the spleen, too, was palpable. Blood pressure 110/65.

**X-ray examinations, March and July, 1955**

_**Ribs:**_ Marked thickening of trabeculae of all ribs. The osteoporotic changes previously seen are not present.

_**Pelvis, lumbar, dorsal and cervical spine:**_ Very marked sclerosis of whole bony structure.
Skull: The multiple islets of increased density, noted two years earlier, now not seen; outer and inner tables and diploic spaces form one continuous undifferentiated sclerotic density.

Humerus, radius and ulna: The sclerotic process has advanced markedly since previous examination. Inner aspect of cortex merges with sclerosed medullary cavity; no clear distinction between cortex and spongiosa. Distal parts of radius, ulna, carpal and metacarpal bones show marked thickening and coarse trabeculation.

Laboratory examinations

Blood urea, blood uric acid, serum chloride, blood glucose, serum cholesterol, total blood proteins, serum albumin, serum globulin and various liver function tests were all within normal limits. Blood sedimentation rate: 45/106 (Westergren). Sternal puncture was unsuccessful.

During hospitalization the skin eruption progressed and besides the typical lesions of urticaria pigmentosa there appeared bluish-white infiltrations of about 1 cm in diameter mainly on the chest and back and a net-like erythema over the upper part of the chest. The patient's general condition deteriorated rapidly; she developed a high temperature and in spite of the immediate start of cortisone therapy, combined with nitrogen mustard, she died on July 25, 1955. Five further blood examinations had confirmed the diagnosis of monocytic leukemia. Shortly before death the leukocyte count had risen to 248,000 cells per cu. mm with 78 per cent monocytes and liver function tests had given the following results: Takata-Ara +, thymol turbidity 5.9 units, thymol flocculation +, cephalin flocculation +, Weltman 8.

Autopsy

Autopsy revealed a terminal bronchopneumonia of the right lung with sero-fibrinous pleurisy. Generalized lymphadenopathy was present, involving also the intrathoracic and intra-abdominal glands; the glands were harder than normal and the cut surfaces revealed homogeneous greyish tissue. The palatine and lingual tonsils were likewise enlarged.

The liver was hard and weighed 2885 gm.; the lobular pattern was well preserved, the portal spaces being markedly enlarged by greyish-white tissue. The spleen, weighing 560 gm., was likewise of firm consistency; the cut surface was homogeneous greyish-red with small hemorrhages in some places.

The kidneys were slightly enlarged and the cut surfaces showed greyish-white foci of various sizes; many hemorrhages were scattered in and around the greyish foci.

The skeletal system showed marked changes (Figs. 3, 4).

The cranial vault measured 6–8 mm in thickness and the cut surface was of a uniformly grey-white color. After maceration in antiformin the diploe was found to be almost completely sclerosed and fused with both tables; however, the inner table was still sharply defined in some places. The internal surface of the bone had a worm-eaten appearance due to innumerable nutrient vessels the entrance points of which were surrounded by hyperplastic bone.
**Ribs:** Following maceration, a slight roughening of the outer surface was seen and the corticalis appeared in many places irregularly thickened, in other places very thin. The marrow cavity was considerably narrowed by sclerosed cancellous bone.

**Lumbar vertebrae:** The marrow was firm in consistency and grey in color, tiny foci of dark-red marrow being only occasionally found. Macerated specimens showed densely packed, thickened trabeculae; the corticalis was extremely thin and appeared incorporated into the hyperplastic spongiosa.

Cross-section through the shaft of the right femur revealed a corticalis of normal thickness and in the marrow cavity greyish-pink fibrous tissue of leathery consistency.

**Histological examination**

Tissues for sectioning were fixed in 10 per cent formalin, in 80 per cent alcohol and in Zenker's fluid. Paraffin sections were stained with hematoxylin and eosin, Van Gieson's stain, Laidlaw's reticulum stain, Heidenhain's azan stain, 1 per cent aqueous solution of toluidine blue, 0.01 per cent aqueous or alcoholic solution of Azure A and with polychrome methylene blue. The bones were decalcified in 5 per cent nitric acid; their staining with metachromatic stains was difficult and succeeded only after treatment of the slides with an 0.5 per cent solution of potassium permanganate followed by oxalic acid rinse. After decalcification of the bones by EDTA (ethylen-diamine-tetraacetic acid) at pH 6.5 according to Hunter and Nikiforuk (9) the sections could easily be stained by the metachromatic stains.

**Skin** (Fig. 1, B): Urticaria pigmentosa lesions near the umbilicus, the left breast and the right thigh revealed, throughout the dermis, a dense cellular

![Fig. 3. Bones after maceration with antiformin. X3.5. A) Lumbar vertebra, composed of thick, densely packed, irregular trabeculae. B) Cranial vault; the diploe is almost completely sclerosed and fused with the outer table. The inner table in this particular area is sharply defined. C) A rib showing the corticalis of the upper surface fused with the sclerosed diploe, and that of the lower surface irregularly thickened.](image-url)
infiltration having an arrangement more tumor-like than inflammatory. The cells were mostly monocytes similar to those found in the peripheral blood of the patient during life; among them typical mast cells were found, being mostly perivascular in location; in different sections the number of mast cells varied from 10 to 40 per cent of all cells present. In addition, a few eosinophiles were scattered among the infiltrations. Congested capillaries, present in large numbers particularly in the upper part of the dermis, were filled with dense accumulations of monotypic cells.

Skin taken from the bluish-white infiltrations and from the net-like erythema over the right breast again showed dense monotypic infiltrations in the dermis and in the subcutaneous fatty tissue, with only occasional admixture of a few mast cells.

Liver: Enlarged portal spaces were filled with cellular infiltrations composed predominantly of monocytes with a lesser number of lymphocytes, eosinophiles and neutrophiles and a few mast cells. Accumulations of monotypic cells were present also in the sinusoids and in some areas around the central veins.

Spleen: Only a few very small lymph follicles were preserved. The pulp was occupied by monocytes which infiltrated also the capsule, the fibrous trabeculae and the walls of the larger blood vessels. In addition, scattered plasma cells, mast cells, eosinophiles, megakaryocytes and macrophages containing granules

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**Fig. 4.** X-ray photographs of macerated post-mortem specimens of the cranial vault, two lumbar vertebrae and a rib showing the marked osteosclerosis.
of hemosiderin were found throughout. No increase in the quantity of reticulum fibers was noticed.

**Lymph nodes** (Fig. 5): In most nodes the normal pattern was completely destroyed and replaced by monotonous infiltrations of monocytes. Amongst these were found mast cells varying in amount from 1 to 10 per low power field and also single megakaryocytes and eosinophilic leukocytes.

Similar monocytic infiltrations of varying intensity were observed in the tonsils, the lymphatic tissue at the base of the tongue, the kidneys, the pancreas, some parts of the epicardium and the adjacent myocardium, the submucosa of the larger bronchi and the peri-bronchial and perivascular tissues of both lungs. Dense infiltrations of monocytes were seen in the various layers of the stomach and intestines, the adrenals and in the episcleral tissues and choroid of the eyes.

The blood vessels of many organs, particularly the veins of the brain and of the thyroid, contained large accumulations of monocytes in their lumina.

**Bones. Cranial vault:** The compacta was very thick and composed of several layers of lamellar bone. The diploe (Fig. 6) was formed by a dense network of thick trabeculae consisting almost entirely of layers of slightly basophilic lamellar bone with here and there thin layers of fibrillary bone.

Many marrow spaces were filled with accumulations of mast cells, lying partly within a delicate network of loose connective tissue (Fig. 7) and partly within dense connective tissue. Other marrow spaces were completely fibrosed and in a few monocytic infiltrations only were observed.

The quantity and staining of the granules in the mast cells were variable. In some cells they were clearly metachromatic and completely filled the cytoplasm,
Fig. 6. Diploe of cranial vault, formed by a dense network of thick trabeculae. These consist of several layers of slightly basophilic lamellar bone. Here and there rests of fibrillar, basophilic bone are still present. The marrow spaces are partly filled with mast cells, partly fibrosed. Hematoxylin and eosin. X48.

Fig. 7. A small marrow space in the skull filled with mast cells lying in a loose network of connective tissue fibers. Toluidine blue. X400.
Fig. 8. Lumbar vertebra. The diploe shows irregular thickened trabeculae which consist in many places of a core of old bone with an apposition of immature, strongly basophilic fibrillary bone. In some places knobs of immature bone include in their centers rests of old spongiosa. The marrow spaces are partly fibrosed and partly filled by cells. Hematoxylin and eosin. ×8 (A); ×35 (B).

Fig. 9. Lumbar vertebra. A) Marrow spaces showing mast cell accumulations and, on the right, fibrosis with mast cell infiltrations. Hematoxylin and eosin. ×33. B) Typical mast cells from one of these marrow spaces. Hematoxylin and eosin. ×580.
while in others the granules were orthochromatic or metachromatic and fewer in number; in some places granules were dispersed extracellularly.

*Lumbar vertebrae* (Figs. 8, 9): Some of the thickened trabeculae were built of mature bone, others of immature bone; mostly they consisted of a slender core of mature bone on one or both sides of which new, strongly basophilic immature, coarse fibrillary bone was apposited in layers of varying width. In some places the immature bone formed round knobs or buds, sometimes with rests of old spongiosa within them. The immature bone contained large osteocytes, irregular in shape and distribution, lying in a matrix of basophilic fibers. In some places the immature bone trabeculae were lined by a thin margin of osteoid.

The marrow spaces were similar to those of the skull; many were filled with accumulations of mast cells, others were fibrosed and some of them contained abundant monocytic cells, intermingled with a varying number of mast cells. Mast cells were also observed lining large, empty vascular spaces (Fig. 10, A). Except for a few megakaryocytes found scattered in the areas of monocytic infiltrations, no active hemopoietic tissue was found. The ribs and iliac crest presented the same histologic picture as the lumbar vertebrae.

Bone marrow from the shaft of the right femur showed large areas of dense fibrous tissue containing, at the periphery, a few small trabeculae of the mature spongiosa. A number of blood capillaries present in the fibrous tissue were lined by a layer of mast cells (Fig. 10, B). Here and there mast cells were also present within the lumen or in a peri-capillary location. A few small monocytic infiltrations were found and also small foci of hemopoietic tissue showing monocytic, myeloid and red cells in different stages of development.

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**Fig. 10.** A) Marrow space in a lumbar vertebra. Tissue mast cells are seen lining large, empty vascular spaces. Toluidine blue. ×360. B) Fibrosed bone marrow of the right femur. Some of the capillaries are lined by a layer of mast cells. Toluidine blue. ×460.
Pathologic-anatomic diagnosis

Urticaria pigmentosa with mast cell infiltrations in skin and bones. Osteosclerosis and myelofibrosis. Monocytic leukemia with involvement of skin, bone marrow, many groups of lymph nodes, tonsils, liver, spleen, kidneys, pancreas, epicardium, myocardium, lungs, stomach, intestines, adrenals and eyes. Bronchopneumonia, and serofibrinous pleurisy of the right lung.

DISCUSSION

The essential features of the case here described, apart from the skin lesions, are the systemic accumulations of mast cells, the myelofibrosis and osteosclerosis and the terminal monocytic leukemia.

The extensive mast cell infiltrations of bones in the present case lend some support to the view that the skin and bone lesions of urticaria pigmentosa are of the same nature (1—7). Mast cell accumulations in bone marrow in conditions other than urticaria pigmentosa have, indeed, been described. Thus smaller accumulations of mast cells have been observed in the bone marrow of patients with generalized or partial bone marrow depression (11—13). It has even been maintained by some that tissue mast cells are present in normal bone marrow (11, 14) but this has been disputed by others (12, 13). Mast cells in bone marrow have never been reported in such abundance as in this case nor in such numbers as in bone marrow smears from previously reported cases of urticaria pigmentosa (7, 8, 10).

The possibility that urticaria pigmentosa is sometimes systemic in nature is also supported by the finding in some cases of mast cell infiltrations in lymph nodes (15) and in various internal organs (3, 7, 8, 10). Of interest in this connection, too, is the description by Degos et al. (16 a—d) and Hissard et al. (17 a—c) of systemic mastocytosis with cutaneous lesions different from those present in urticaria pigmentosa.

In the present case mast cells were occasionally seen replacing capillary endothelial cells. This incidental observation, while not contradicting the generally accepted view that mast cells originate from undifferentiated mesenchymal cells in the adventitia of blood vessels (18, 19) or from fibroblasts (17, b) may signify that mast cells perhaps also arise from endothelial cells.

The possibility of a relationship existing between the mast cell infiltrations in the bones and the myelofibrosis merits consideration. Riley (20 a, b) has reviewed earlier work on the role possibly played by mast cells in the formation of fibrous tissue; more specific mention may be made of in vitro experiments (7, 21) which seem to show that heparin, which is known to be produced by mast cells (20 a), promotes the formation of collagen fibers. While this speculation seems attractive, it cannot be said to be substantiated in view of the dearth of information on the bone marrow in urticaria pigmentosa and in view also of the great variety of blood diseases associated with myelofibrosis without increase in the number of mast cells.

The determination of the sequence of events resulting in myelofibrosis and osteosclerosis in our case presents difficulties. It is known that osteosclerosis
and myelofibrosis may occur in a number of blood diseases such as leukemia, polycythemia vera and anemias of various types (22–25); this has been explained by some authors as an event in the progress of these blood diseases towards healing or scarring (25–30). Our patient appeared stigmatized for the development of the terminal leukemia two years before death when a monocytosis of 17 per cent was found in the peripheral blood. One might presume that during this period the patient suffered from chronic aleukemic monocytic leukemia which caused the myelofibrosis. However, this is not confirmed by the clinical findings, namely absence of lymphadenopathy and absence of a palpable liver or spleen until relatively late in the course of the disease. Furthermore, the monocytic infiltrations in the internal organs, where fibrosis was absent, were on the whole more massive than in the bone marrow. In the bone marrow itself, monocytic infiltrations were not present in areas of fibrosis.

It is, therefore, possible that in our case it was not the leukemia which produced the myelofibrosis but that progressive myelofibrosis had stimulated extra-medullary hemopoiesis, eventually leading to monocytic leukemia; it is recognized that primary myelofibrosis may be followed by proliferative disorders of the blood elements (22–25). Alternatively, it is possible that both the myelofibrosis and the leukemia were results of proliferative activity of descendants of multipotent mesenchymal cells (25, 32, 33, 34). In either event, the myelofibrosis and osteosclerosis, in turn, may have been the direct result of tissue mast cell accumulations in the bone marrow as an expression of systemic urticaria pigmentosa. Whether the urticaria pigmentosa was also causally related to the leukemia is unknown. Leukemia as a rare complication of urticaria pigmentosa has been reported by Balbi (25), Hermans (36) and Efrati (37), and instances of pseudoleukemia have been observed by Touraine et al. (38) but these scattered reports do not permit of any conclusions to be drawn.

It is possible that the underlying lesions also in other reported cases of urticaria pigmentosa with roentgenologically detected bone changes consist of myelofibrosis, osteosclerosis and mast cell accumulations. Since bone changes of this kind are known to be connected with various blood diseases the hematological investigation of such cases of urticaria pigmentosa would seem to be indicated.

SUMMARY

A case of urticaria pigmentosa with disseminated bone involvement is reported. The case was followed for two years prior to the patient’s death from monocytic leukemia.

Post-mortem examination revealed mast cell accumulations in the bone marrow of the affected bones, suggesting that the bone lesions were of the same nature as the skin lesions. In the bones the mast cell accumulations alternated with widespread myelofibrosis. Osteosclerosis was also present and was characterized by extensive formation of immature bone.

Infiltrations of monocytes were present in the skin, the internal organs and the bone marrow.

The possibility that the mast cell accumulations were causally related to the
myelofibrosis is discussed, as also that the leukemia was not merely coincidental but causally related to the progressive myelofibrosis.

Tissue mast cells replacing the endothelial lining of blood capillaries were observed.

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