Studies on Mucopolysaccharide in Skin Diseases

I. Treatment of Urticaria Pigmentosa with Hyaluronidase

By

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Cases of urticaria pigmentosa, first described by Nettleship in 1869, have been reported in 900 instances in Europe and the United States and in nearly 100 in Japan, since first reported by Tôyama in 1906, but the disease is as yet regarded as “rare.” It is generally more prevalent by infants, but it may befall subjects of any age. As Unna has pointed out, an increase in the epidermal pigmentation and an infiltration of mastcells in the upper layer of corium are specific symptoms of importance, so that it is sometimes called mastcytoma or mastcellnaevus, but its pathogenesis and etiology are not yet clarified to date, some looking upon it as naevus or benign tumor, while others see reactive anomaly or reactive inflammatory variation in it. Consequently, no therapeutic method could claim sure efficacy against the disease. Recently, we have met with two cases of this disease, in which we found histologically, a large quantity of hyaluronic acid or heparin secreted by abundant mastcells, upon examination under utilization of Lison’s metachromatic staining, so that we thought of trying administration of hyaluronidase, by which we have succeeded in bringing about a prompt and sure relief, as reported below.

Case 1. A male, age 10 months, first seen on Dec. 27, 1951, otherwise in good health and with no family history to mention. In the first part of Nov. 1951, he had disseminated yellow eruptions in size of millet seed on both legs, without any visible immediate occasion, which gave hardly any feeling of itching and disappeared in a week. In Dec. of the same year, pink-colored eruption of sizes varying from pin-head to Indian beans broke out on his left cheek and in a few days spread all over his body, causing vehement itches so that he complained of want of sleep.

Present status: Patient is a bottle fed infant, normal in growth and viscera, both liver and spleen impalpable and no swelling in lymphatic glands. The eruption is disseminated all over the body, except the haired...
part of the head, being most conspicuous on the limbs. The most affected parts were the flexor surface of the legs and the upper arms, the back coming next, the cheeks and the side necks being also a little affected. The eruption consisted of light yellow-brown papules of sizes varying from pin-head to lentils, with distinct boundaries, elevated a little over the skin surface, flat-surfaced and of wax-like lustre, showing no diascopic discoloration. Its dermographia was positive, and by histamine scratch test, redness and swelling were tardier, both in appearing and fading, on the papules than on the normal skin, showing a lag in the time of reaction.

Laboratory examination: Blood Wassermann's reaction negative; red cell count, 4.2 millions; white cell count, 14,400; hemoglobin, 72% (Sahli); neutrophil leucocytes, 28%; eosinophil leucocytes, 2%; lymphocytes, 61.1%; monocytes, 9% and blood coagulation time, 6 min. 40 sec. All the above normal. Phosphatide in serum lipoid, 204.48 mg%; free cholesterol, 137.70; total cholesterol, 162.18; esterized cholesterol, 24.48; neutral fat, 192.37; total lipoid, 574.21, which is a value larger than the Enickson-Williams standard.

Case 2. A male, age, 38, seen first on April 1951. Family history; late mother and brother had ichthyosis, the former having brown macules as seen by the patient. Patient married 7 years ago. Childless.

Past history: At the age of 16, had dermatitis occasioned by touching raw lacquer, and at the age of 27, suffered from toxicodermia upon eating sardines. Became conscious of yellowish brown macules of sizes varying from pin-head to half a grain of rice on his breast, when he was 29 years old, and sometimes felt slight itching. In the following year, the macules spread all over his body, growing especially conspicuous on his limbs and back. Upon warming himself or taking alcoholic drinks, the macules became markedly pigmented, and the itchy feeling grew stronger. At present, he complains of strong feeling of heart-burns and belching, upon feeding upon sardines and mackerel pikes.

Present status: Good nutrition and stature; viscera, normal; liver and spleen, impalpable; lymphatic glands in cervix and in cubital regions swollen to the size of Indian bean and millet seed respectively; eruption observed on the whole body except on the face, palms and soles, especially in large number on the extensor surface of the limbs. The eruption consists of typical brown macules, which are flush with the skin and readily reddened upon rubbing, carrying up the pigmenetary macules thereon in swells, blurring the boundaries of the pigmenetary macules. In 20 min. or so, the redness disappears, restoring the distinctness of the pigmenetary macules. Dermographia, positive; histamine scratch test shows retarding of redness and swell, both in developing and disappearing, recording a
lag in reaction time.

Laboratory examination: Mantoux's reaction, positive; blood sedimentation rate, 3 mm. (1 hr.) and 7 mm. (2 hrs.); blood Wassermann's reaction, negative; red cell count, 5.7 millions; hemoglobin, 82% (Sahli); white cell count, 7,200; lymphocytes, 34%; monocytes, 14%; eosinophil leucocytes, 8%; neutrophil leucocytes, 44%; blood pressure, 120–64; Aschner's reaction, positive; pilocarpine test, positive; both adrenalin and atropine reaction negative; viz vagatonia presumable; Takada's reaction slightly negative and urin urobilinogen test positive, indicating functional disturbance of liver; phosphatide of serum lipoid, 151.94 mg%; free cholesterin, 57.12; total cholesterin, 129.54; esterized cholesterin, 72.42; neutral fat, 106.69 and total lipoid, 433.08, all approximately normal.

Histological observation: A pigmentary macule on the patient's lower region of right scapula was excised and stained with hematoxilin-eosin and under the method of Weigert. Also Lison's metachromatic staining of mucopolysaccharide was applied. The picture was decidedly typical, increase of pigment was conspicuous in the basal layer of the epidermis, and a multitude of mastcells was observed around the blood vessels in the upper layer thereof. The numerous granules of mastcells stained red, and by the scattering of the red granules upon addition of hyaluronidase to the section, existence of hyaluronic acid was assumed.

Therapy: In consideration of the histological observations above, the two subject patients were given injection of hyaluronidase (2,000 VUM) twice every week, either interdermally or subcutaneously in loco. The Case 1 lost the itching on the second day after the second injection, and began to sleep comfortably. The swell of the eruption began also to decrease gradually thereafter, some of the macules disappearing after the 6th injection, and when the 17th injection was given, the pigmentary macules almost entirely faded, leaving no itching at all. By the Case 2, the swells remarkably withdrew after the 5th injection, only a slight dermographia being left observable. With 15 injections the pigmentary macules faded visibly. Both the cases were judged cured to all intents.

COMMENT

The existence of proliferation of mastcells, the pathogenetic feature of the subject disease, is also the center of contention, some regarding the proliferation as the specific symptom of the disease, while others deny it. But the number of cases which showed a proliferation of mastcells is in an overwhelming majority, as shown in Hayami's statistics on the incidence of this malady in Japan, which says that in his 77 cases of occurrence in total, only 2 were free of such a proliferation. Though mastcells were
believed to be generated by repetition of stimuli, in former times, their biological significance cannot be regarded as yet as clearly established. Recently, Asboe-Hansen\(^2\) published his interpretation that “Mastcells are the producers of hyaluronic acid, and are interpreted as the peripheral transmitters of hormonal action on the connective tissue, perhaps by way of a precursor resembling heparin.” and “Mastcells may also influence the hyaluronic acid-hyaluronidase system by the secretion of heparin.” based upon a long series of observations, while Holmgren and Wilander, Luigi,\(^3\) Leclercq,\(^4\) Jorpers and others announced their opinion that the function of mastcells is the secretion of heparin and regarded them as heparinocytes. Prakken and Woerdeman,\(^5\) in agreement with Battezatti, Hisard, Moncourier and Jacquet, assume that “mastcells have an important function in the metabolism of mucopolysacharides and perhaps, they may contain and release both heparin and hyaluronic acid and eventually effect the metabolism of the latter into heparin,” while Glick and Sylven contend that heparin is a hyaluronidase inhibitor. If mastcells secrete hyaluronic acid, the numerous red granules mentioned above in the histological observation must have been composed of hyaluronic acid. Recently, Degos, Hewitt and Morter\(^6\) in Hospital Saint-Louis reported that no noticeable change was brought about by injection of hyaluronidase in the locally involved skin of an urticaria pigmentosa patient, but it may be pathogenetic interest that we succeeded in obtaining favorable results in two cases by repeated injection of hyaluronidase. The fact that our Case 2 had no child after 7 years in matrimony seems to suggest the problem of semen-hyaluronidase, and even the presumption that patients liable to urticaria pigmentosa are constitutionally under a specific influence of hyaluronidase. Furthermore, the occurrence of this rare disease in a family seems to indicate even an influence of hereditary genes on the varying predominance of hyaluronidase, if we borrow the physiogenetic expression of Goldschmidt.

**SUMMARY**

As we had ascertained the existence of a quantity of hyaluronic acid in the histologically abundant mastcells of two cases of urticaria pigmentosa, by means of Lison’s metachromatic staining, we applied injection of hyaluronidase in their involved skins interdermally or subcutaneously, and had the satisfaction of seeing both the cases cured to all intents. These results, we believe, may give some suggestions on the pathogenesis of this disease.

**References**

1) Hayami, Act. Dermat. (Kioto), 1944, **43**, 1, 125.