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Ochronosis : with report of an additional case

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OCHRONOSIS WITH REPORT OF AN ADDITIONAL CASE

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Ochronosis, according to Duncan[1], is the clinical state in which there is a varying degree of darkening of the cartilages, the ligaments, and the fibrous structures of the body and is not a specific entity in that the discoloration has more than one cause. It is very closely related to alkaptonuria and to the use of phenol over a long period of time.

Oppenheimer and Kline[2] classify ochronosis as: (a) That type due to the circulation in the blood of certain aromatic compounds with the excretion in the urine of homogentisic acid, (b) That type due to the circulation in the blood of certain aromatic compounds with the excretion in the urine of melanin, and (c) That type due to the external use of phenol.

Scribonius, as quoted by Pomeranz[3], reported an early case of alkaptonuria:

> "The patient was a boy who passed black urine and who at the age of fourteen years was submitted to a drastic course of treatment, which had for its aim the subduing of the fiery heat of the viscera which was supposed to bring about the condition in question by charring and blackening his bile. Among the measures prescribed were bleeding, purgative baths, a cold and watery diet and drugs galore. None of these had an obvious effect and eventually the patient who tired of the futile and superfluous therapy resolved to let things take their natural course. None of the predicted evils ensued, he married, begot a large family and lived a long and healthy life, always passing urine as black as ink."

Historically, Rudolph Virchow [4] made the first report on ochronosis in the literature in 1866 in a 66-year-old male dying of an aneurysm of the ascending aorta. Two more cases were reported in the 1890's and Osler[5] reported two more in 1904, being the first writer to note ocular involvement. Poulsen[6] in 1910 reported nine more. Oppenheimer and Kline[7] in 1922 reviewed the literature and found forty cases to have been reported and added one of their own. Smith[8] again reviewed the literature in 1942 and found eighty-two cases including four of his own. A further review of the literature shows that up through 1948 nine more cases have been reported [9] [10] [11] [12] [13] [14]. The case reported here has not been reported in the literature.

Oppenheimer and Kline[15] tabulated the forty-one cases then reported and found that nineteen were males and that twenty-two were females, the average age at diagnosis being fifty-one and the youngest being diagnosed at twenty-five.

Virchow's [16] original report mentioned pigmentation of all cartilages, fibrocartilages, and, to a less extent, of all ligaments, tendons, perichondrium and periosteum. Microscopically, he observed

ochre-colored granules in the extracellular matrix of the cartilages examined and he therefore named the entity "ochronosis". Poulsen[17], in his authoritative one hundred and eighty-nine page monograph on ochronosis and study of nine cases, reports that the pigment was deposited principally in the cartilages, especially those of the air passages and of the larger joints and that the cartilages of the smaller joints were usually not pigmented. He also reported that the fibrocartilages, such as the intervertebral disks were also involved; he did not find as great a deposit of pigment in perichondrium, periosteum, tendon, bursa, or joint capsule. The bones showed pigment in some cases. He found pigment in endocardium, beneath the intima of the larger vessels, and in the kidneys, rarely in such locations as bits of cartilage in the tonsils, the connective tissue of the lung and thyroid gland, in the fatty tissue around the perichondrium, and in the dura. Pigment was frequently found in the sclerae, epidermis, and occasionally in the nails. Pigment masses were found occasionally in the prostate although the real character of the masses is questioned. Studies of cartilage showed that cells in viable cartilage were not pigmented whereas

degenerative cells were not deeply pigmented. According to the state of viability of the cartilage the pigment may be intracellular or extracellular.

Oppenheimer and Kline[18] carefully studied the kidney and suggest that excretion is by the cells of the proximal convoluted tubules and that there is partial reabsorption by cells of the loop of Henle, distal convoluted tubules, and the collecting tubules and that there is a transformation of the pigment into a more granular form. The stain most satisfactory for demonstrating this in the sections is silver nitrate.

Oppenheimer and Kline further suggest that the arthritic changes are specifically due to the irritation produced by the deposited pigment.

These authors describe radiographic changes as: (a) Calcification of intervertebral disks, (b) Lipping of the lower and upper borders of the bodies of the vertebrae (spondylitis deformans), (c) Calcification of the interpubic disk, (d) Lipping of upper portion of acetabulum with a large amount of calcification around the greater trochanter along with some bony excrescence at its base, (e) Complete obliteration of the frontal sinuses, (f) Some calcification along insertion of upper portion of interosseous membrane in lower leg, (g) Upper portions of

of the humeri showing a condition that is usually seen in osteitis fibrosa, i.e., rarefaction, lack of clear demarcation between the compacta and spongiosa and beginning cystic degeneration.

Pomeranz, Friedman, and Tunick[19] reported on two cases and found: (a) Universal calcification of the intervertebral disks, (b) Narrowed shoulder joints and an eburnated glenoid with mushroomed humeral heads with circular areas of resorption on the articular surfaces combined with calcification of the tendons origin , (c) Ears showing calcium in the helix, and (d) Calcification of insertions of quadriceps tendons.

Smith[20], in his review of the literature, stressed the eye changes in ochronosis, the changes consisting of scleral pigmentations in the palpebral fissure, pigmentation of the conjunctivae, and sometimes involvement of the corneal periphery. Smith theorizes that the parts affected by this pigmentation are exposed to the catalytic action of light.

Skinsnes[21] reports a case where ochronosis of the sclera was generalized and misdiagnosed as melanosarcoma with resultant enucleation of the eye.

Peters and Van Slyke[22] feel that the alkaptonuric state has been of much aid in obtaining an understanding of the intermediary metabolism of phenylalanine and tyrosine. They define alcaptonuria as that state where homogentisic acid, 2:5 dihydroxyphenylacetic acid, appears in the urine, and that it is accompanied by ochronosis in its severer forms. These authors also note that alcaptonuria is an hereditary disorder.

These authors further note that alcaptonuria is aggravated by the administration of either phenylalanine or tyrosine and that the defect is wholly in the reactions where homogentisic acid is oxidized, the acid being an intermediate in the phenylalanine and tyrosine. It can be shown in the laboratory that phenylalanine, tyrosine, and homogentisic acid when perfused through the surviving livers of animals, form acetoacetic acid. Gibson and Howard, as quoted in Duncan[23] showed that liver extract, when given intramuscularly, will free urine of homogentisic acid for from eight to ten hours. Duncan concludes that there is the lack of a catalyst for a specific stage in the breakdown of phenylalanine and tyrosine.

In its early stages there are no symptoms of ochronosis. Kolmer[24] mentions that alcaptonuria may

first be noted in a child when diapers saturated with urine are allowed to stand for a few hours and then darken. However, as the destruction of cartilage ensues there are symptoms of the involvement of the joints. Changes in color of the sclera, ears, nose, cheek are likewise helpful diagnostic aids. There may be widespread pigmentation of the skin as reported by Christian[25]. This author mentions one case where there was black discoloration of the skin over nose and cheeks with the beginning of the same change in the hands. Usually there is marked arteriosclerosis in these individuals probably because of the involvement of the intima of the arteries and arterioles.

The laboratory diagnosis of this disease is most simple. Fishberg[26] has reported a unique test for the presence of homogentisic acid in the urine. In this test a drop of urine is made alkaline with sodium hydroxide or potassium hydroxide, drop placed on regulation sensitized photographic printing paper and wherever it touches the paper, the paper is turned coal black. In eight years of her experience no other substance was found in urine that would produce this reaction. She postulates that this is an oxidation-reduction reaction and due to the close relationship of homogentisic acid to hydroquinone.

Homogentisic acid reduces Benedict's solution and therefore may confuse the issue with diabetes mellitus or renal glycosuria. Duncan[27] asserts that urine that has been alkalinized with sodium hydroxide and then shaken in a dark room will fluoresce because of the oxidation of the homogentisic acid. The simplest test of all is simply to allow the urine to stand in the laboratory in the specimen bottle. The bottle of urine will start to discolor from the top on down and usually will be altogether brown or black in twenty-four to thirty-six hours. This process may be hastened by making the urine alkaline with sodium or potassium hydroxide. Blood may show a nonspecific fixation of complement, therefore the results of Wassermann tests must be judged critically.

The treatment mentioned by Duncan is that of rather large doses of ascorbic acid. It is claimed that this treatment will arrest the discoloration.

REPORT OF A CASE

Note: This patient was told in 1945 that he had ochronosis by a physician at Fort Leavenworth, Kansas. There is no report in the literature on the case as of the end of 1948.

The patient is a forty-eight year old white male, by occupation a retired staff sergeant of the army.

Present Illness:

1. In 1942 patient began to suffer with aching and stiffness in the right knee, right shoulder, and in the lumbar region, the aching and stiffness, with some limitation of motion, having been with him constantly since onset. Occasionally he experiences knifelike pains in the involved areas which are relieved by the application of hot packs.
2. Patient has complaint of suboccipital headaches present on arising for the last year. Headaches leave after an hour or so of activity.
3. Intermittent claudication, right lower extremity, for the last year.

Past History (significant):

1. Kidney stone of a gray color passed in 1934, with some bleeding.
2. Dark spots on sclerae in 1945 which disappeared after a few months.

Physical Examination (contributory):

Ears: Antihelix of both ears of a slate blue color.

Lip : Fungating growth of lower left lip. Wedge resection done and pathological diagnosis of squamous cell carcinoma made.

Cardiovascular: Systolic pressure of two hundred and twenty, diastolic pressure of one hundred and forty, rate is ninety-two. Chest otherwise negative.

Musculoskeletal:

Motion of lumbar spine limited in all directions.

Extremities:

Limitation of motion of right knee joint to about forty-five degrees. Muscle groups inserting below knee contract and relax involuntarily. Arthritic lipping about knee and ankle. Tendons on dorsum of right foot leading to great toe somewhat contracted.

Right shoulder has a limit of forty-five degrees of abduction.

Neurological:

Decreased sensation to pinprick over areas of third, fourth, sixth, and seventh cervical, and first dorsal. Areas of fourth and fifth

lumbar and second, third, fourth, and fifth sacral nerves also have decreased sensation to pinprick. Remainder of neurological not contributory.

Radiographic Findings:

1. Calcium deposits in antihelix of both ears.
2. Marked calcification between all lumbar vertebrae.
3. Osteoporosis, generalized.
4. Arthritic lipping, right knee joint.
5. Right shoulder: Lack of clear demarcation between compacta and spongiosa.
6. Feet: No gross changes noted.

Laboratory Findings:

1. Negative Kahn.
2. Urine turns black on standing for twelve to twenty-four hours.
3. Urine doesnot fluoresce in dark after addition of sodium hydroxide.
4. Blood calcium, blood phosphorus, and alkaline phosphatase all normal. Complete routine blood work negative.
5. Daily homogentisic acid determinations for five days for a twenty-four specimen showed an average of 3.26 grams with a range of from 2.12 to 3.96 grams per day.

Electrocardiographic Findings: Within normal limits.

Basal Metabolic Rate: Negative sixteen on two different occasions.

Clinical Impression:

1. Ochronosis with arteriosclerotic hypertensive vascular disease.
2. Osteoarthritis, right shoulder and right knee.
3. Calcification of lumbar intervertebral disks and of the antihelix of both ears.
4. Hypothyroidism.

SUMMARY

The clinical entity of ochronosis has been reviewed. The first case was reported by Virchow in 1866. An earlier case of alkaptonuria from the sixteenth century has been cited.

The number of cases has been tabulated as reported in the literature and found to be ninety-one as of the end of 1948.

The relationship of alkaptonuria to ochronosis has been pointed out in that ochronosis is but the end result of lifelong alkaptonuria. A stricter classification shows that there are three types of ochronosis: (1) Presence of aromatic compounds in the blood with excretion of homogentisic acid in the urine, (2) Presence of aromatic compounds in the blood with the excretion of melanin, and (3) Presence of aromatic compounds in the blood with excretion in the urine of homogentisic acid due to prolonged topical use of phenol.

Experimental evidence shows that there is a breakdown in the oxidation of tyrosine and phenylalanine thereby giving rise to circulation of certain aromatic substances in the blood responsible for the deposition of pigment in the tissues and excretion of homogentisic acid in the urine.

Pathologically ochronosis results in pigmentation of ligaments, tendons, cartilages, and skin. The sclerae may show areas of pigmentation which have been confused with melanosarcoma.

Radiographic changes show, typically, calcification of intervertebral disks, osteoarthritic changes in the larger joints, and calcification within the anti-helix of the ear.

Symptoms are changes in color of the skin, cartilages of the ear, arthritis of the larger joints, and discoloration of the sclerae.

A case of ochronosis has been presented. The case has typical changes in color of the ear cartilages, osteoarthritic change, and calcification of intervertebral disks in the lumbar region. The case shows homogentisic acid in the urine with typical darkening of the urine on standing.

A case where enucleation of the eyeball was done because of misdiagnosis of an ochronotic globe is presented out of the literature. Present case did at one time show pigmentation of the sclera although it later disappeared.

CONCLUSION

Ochronosis is either becoming more common or is being diagnosed and reported more frequently. In the period of thirty-four years from 1866 to the turn of the century only three cases were reported whereas in the five year span through 1943-1948 nine cases were reported.

Ochronosis is a relatively benign condition but it has been noted by some authors that there is an increased incidence of hypertensive vascular disease in these patients. This is probably due to the deposition of pigment sub-intimally in the larger arteries and arterioles which accelerates the normal arteriosclerotic process.

The opthalmologist should be especially aware of this entity as an ochronotic globe has been enucleated because of a misdiagnosis of melanosarcoma.

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