

Ochronosis

Report of a Case with Associated Disease of Adrenals

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OCHRONOSIS is a rare condition first described by Virchow (1) in 1866. The condition he found at autopsy was characterized grossly by deposits of light, gray, brown, or black pigment in cartilages, ligaments, tendons, and large blood vessels. Microscopically the pigment appeared uniformly yellowish-brown or ochre colored, hence the name ochronosis, given by him. Virchow believed the case to be merely a striking example of more frequent lower grades of ochronosis since he had sometimes observed yellowish or brownish discoloration in the semilunar cartilages of the knee joint, costal and bronchial cartilages of old individuals with deposits of pigment homogeneous and diffuse, in the intercellular substance. He suggested that hematin derivatives of the blood might be deposited in areas having a poor vascular and nerve supply but exposed to irritation.

Survey of the literature shows that 41 cases have been reported. The studies made indicate that the cause is due to disordered metabolism of phenol or some of its derivatives; with pigmentation of cartilages, skin, fibrous tissues and almost any area of degeneration, particularly atherosclerotic plaques, masses of albumin or

concretions; further characterized by darkening of the urine from the presence of alcapton, derivatives of phenol, or melanin.

ETIOLOGY

Etiologically the cases reported fall in three groups:

1. Ochronosis caused by alcaptonuria.
2. Ochronosis caused by use of phenol.
3. Ochronosis due to other causes than alcaptonuria or phenol.

Ochronosis due to alcaptonuria is thought to be a congenital metabolic disorder of intermediary protein metabolism. The first explanation of the true nature of ochronosis was advanced by Pick (2) who considered that phenol bodies were changed into melanin pigment by the action of the oxidizing ferment tyrosinase. This view is, in the main, still held. Eighteen of the cases recorded are definitely in this group, two others probably had alcaptonuria and another showed melanuria and probably alcaptonuria. The above figures are based on the tables of Kolaczek (3) cited by Oppenheimer and Kline (4). Janney's (5) careful analysis of the pigment in the last reported case, and the incomplete analysis in some of the cases

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within this group, indicates that the number is probably too high.

In ochronosis due to the use of phenol the metabolic disorder is acquired.

As a possible explanation for the obscure cases Janney (5) says:

Pigment formation from higher compounds such as polypeptids, closely related to protein, becomes of interest. It seems not unlikely from the number and complexity of the split products of such melanins which have been observed that this class of the black pigments may indeed be of very complex constitution. Their tyrosin content may, however, be responsible for the development of the pigmentation owing to the oxyphenyl group contained in this amino acid. The tumor and other protein melanins among which the example here described apparently belongs probably owe their origin to a metabolic anomaly of this nature.

Abderhalden and Guggenheim (6) have, more recently than Pick (2) studied the action of tyrosinase in the formation of melanin. Their work showed that melanin pigment is formed by the action of the ferment on such substances as homogentisic acid, phenol compounds, amino acid tyrosin and tyrosin-containing polypeptids. The rôle of ferments in pigment formation is not definitely known. Tyrosinase is, however, known to be widely distributed in animals and is probably normally present in their bodies. This ferment acting on the chromogenic substances mentioned, present in more than normal amounts within the body may, Janney (5) believes, be the cause of ochronosis.

The most recent, and one of the most comprehensive, studies of ochronosis is that made by Oppenheimer and Kline (4) in 1922. A separate study of the chemical analysis of the

urinary, cartilage, and concretion pigments in this case was made by Janney (5). His study is particularly valuable because of the complete chemical analysis. In the case studied the ochronosis was due neither to alcaptonuria or phenol, and a melanin was isolated from the urine pigment. The studies made previously by others in cases where alcaptonuria and phenol could be excluded are less complete than his. Analysis of this case has definitely established a third class of cases of ochronosis with melanuria. Another important point emphasized by him is the fallacy of making a diagnosis of alcaptonuria without the identification and isolation of pure homogentisic acid.

REPORT OF CASE

In reporting this case credit for the diagnosis of ochronosis is given to Dr. A. S. Warthin, Professor of Pathology, University of Michigan. At necropsy, although impressed by the extensive pigmentation of the cartilages, the changes in the adrenal glands were so striking that the writer thought it a very unusual case of Addison's disease and it was not until the findings and sections were sent to Dr. Warthin that the correct diagnosis was established. The microscopic diagnosis is, in general, identical with his.

Unfortunately, because ochronosis was not suspected at the time, the urine was not examined and it is therefore impossible definitely to classify this case, except to say that the ochronosis was not due to phenol.

One outstanding feature of the case however makes it well worth reporting, namely, the association of exten-

sive disease of the adrenal glands. The lesions in the adrenals are so marked that it is difficult to believe there was not, in addition to the ochronosis, an associated adrenal insufficiency. Scott (7) mentions that ochronosis has been observed in connection with disorders of the suprarenals. The only reported case found is that of Pope (8). In his case there was "pulmonary tuberculosis and disease of the adrenal glands." The color of the urine was considered to be due to carboloria since the patient had used phenol as a local application for a long time. One instance of Addison's disease in which the x-ray revealed calcification of the adrenals has been reported by Rolleston and Boyd (9) but no mention is made of pigmentation of aural or nasal cartilages to indicate the presence of ochronosis.

CLINICAL HISTORY

The man died without medical attention and the cause of death was therefore determined at Coroner's autopsy.

The following meager information was obtained from the family of the deceased:

W. D. was of Irish extraction; his exact age was unknown but was thought to be about eighty-five. He was a farmer until he retired twenty years ago. In early childhood his hands and face were severely burned by boiling water, causing the scars seen at post-mortem examination. He was married and had several living children, none of whom had alcaptonuria or any abnormal pigmentation of the skin or cartilages. There is a negative history of the use of phenol. The deceased had never mentioned, nor had any of the family ever noted, any abnormality of the urine. The

family considered that his health was good for a man of his age.

On the day of death he complained of pain in the chest; this was relieved by hot applications but he sank rapidly and died within a few hours.

The following additional information was furnished by Dr. William F. Kaiser:

Although he had been the family physician for a number of years he had never been called to see Mr. D. until three days before death. At this time, during the course of a visit to another member of the family, Mr. D. complained of sore throat and the physician was asked to examine him. Examination disclosed nothing of impor-



FIG. 1. COSTAL CARTILAGES, SHOWING COAL-BLACK PIGMENTATION

tance. No pigmentation of the buccal mucous membrane was noted at the time. The deceased had often complained of "rheumatism" but had never sought treatment for the condition.

NECROPSY FINDINGS (ABRIDGED)

W. D., coroner's case No. 9045. Necropsy performed fifty-one hours after death.

The body is that of a poorly nourished white male about eighty-five years of age, measuring 61 inches in length and weighing approximately 110 pounds. On the left side of the face is an old whitish scar which in its contraction has pulled the eyebrow upward. The eyes are not examined. There is slight blackish pigmentation of the skin of the nose; otherwise there is no discoloration of the face or ears. The gums have

been sutured by the embalmer and the oral cavity is therefore not accessible for examination. The front teeth are absent. The right hand is the site of a large white scar involving both dorsal and palmar surfaces; the thumb is adducted and the entire hand is somewhat contracted. There is no pigmentation of the scar tissue. On the dorsal surface of the left hand is a scar which shows a few pin-head-sized areas of black pigmentation. The skin over the upper parts of the scapulae reveals dark areas of pigmentation.

When the ribs are exposed they appear

the line of attachment of the anterior cusps of the pulmonary valve there is blackish discoloration in and beneath the endocardium. The aortic leaflet of the mitral valve is thickened by atherosclerotic plaques (fig. 2); two of which are jet black. The bases of the aortic valve cusps are calcified and these areas too are black. The cusps are slightly thickened but regular. An irregular area 3 by 5 cm. in the ascending aorta is slate-gray to black. A number of small atherosclerotic plaques in both ascending and entire descending aorta are intensely black. Cut surfaces of the aorta



FIG. 2. PIGMENTATION OF CALCIFIED PLAQUES IN MITRAL VALVE

Slate-gray to black ochronotic pigmentation of ascending aorta. (Arrows indicate various areas.)

much darker than normal; the costal cartilages are black as charcoal (fig. 1). When sectioned they are in most instances black throughout; others are black except for the central portion which is yellowish-brown. The perichondrium covering them is calcified. The cartilages are very brittle. The cartilages of the sterno-clavicular joint are also black. Both pleural cavities are obliterated by fibrous adhesions. The heart is small, weighing 300 grams. The myocardium is slightly brownish. Along

disclose deposits of black pigment both in the intima, in association with atherosclerotic plaques, and in the outer media. At the tips of both papillary muscles of the mitral valve are pin-head sized areas of black pigmentation. The tricuspid valve is unchanged. Both main coronary arteries are moderately sclerotic and show black pigmentation both in the intima and outer media.

The cartilaginous rings of the trachea and main bronchi are black, the pigment

being localized in the perichondrium and outer portion of the cartilage (fig. 3). Several of the tracheobronchial lymph nodes



FIG. 3. OCHRONOTIC PIGMENTATION OF TRACHEOBRONCHIAL CARTILAGES

contain miliary tubercles with evidence of partial healing; anthracosis is quite marked. Posteriorly and at the bases the lungs are dark and boggy. Sections disclose edema, passive congestion and early bronchopneumonia in the bases. The intervertebral discs are black. There is some overlapping of the bones of the vertebrae.

The right adrenal is entirely calcified;



FIG. 4. ADRENAL GLANDS

Actual size. Right (smaller) entirely calcified. Half of left calcified.

when broken the inner portion appears slate-gray. No adrenal parenchyma remains, nor is there any evidence of accessory adrenal substance in this region. The left adrenal is half calcified. The capsule

of the remaining part is thickened. Lipoid in the cortex is abundant. No accessory glands are found in this region. The right adrenal weighs 3.7 grams; the left 3.72 grams (fig. 4). Both kidneys are small,



FIG. 5. PATCHY OCHRONOTIC PIGMENTATION IN DURA MATER

each weighing 112 grams. The cortex of each is thin, irregular, and the pelvic fat is increased. No pigmentation is observed in the kidneys. The urinary bladder is moderately distended with dark amber colored urine. Sections through the prostate expose a number of very small black concretions and one larger concretion 1 cm. in diameter.



FIG. 6. FINE GRANULAR PIGMENTATION IN PERICHONDRIAL CELLS OF BRONCHIAL CARTILAGE

Slight pigment deposits in cartilage cells nearest lumen. Low power.

The spleen is adherent to the parietal peritoneum by fibrous bands; it weighs 68 grams. The liver is small and adherent to the peritoneum by old fibrous adhesions; it weighs 577 grams. In the posterior wall of the first portion of the duodenum there is a firm whitish nodule 2 centimeters in diameter, located in the submucosa and covered by mucosa.

MICROSCOPIC DIAGNOSIS

Heart. Atrophy and slight brown atrophy. Serous atrophy of subepicardial fat. Marked sclerosis of larger coronary arteries with pigment cells, chiefly in the media, more marked toward the adventitia, but also some in the thickened intima in association with atherosclerotic plaques,



FIG. 7. DIFFUSE BROWNISH PIGMENTATION OF COSTAL CARTILAGE CELLS

Living cells unpigmented. Low power

The bones of the calvarium externally are brownish. Internally several streaks of black pigmentation are seen. In the falx cerebri are a number of streaks of black pigment (fig. 5). There is slight edema of the leptomeninges. Except for slight atrophy no changes are found in the brain; it weighs 1370 grams.

The larger joints are not examined.

especially in areas of greatest degeneration. One area of myofibrosis with diffuse yellowish-brown pigment in the cells found. Some pigmented cells in the endocardium.

Aorta. Marked atherosclerosis with calcification. Numerous large cells in the media showing either calcification or granular pigmentation. One small area of active mesaortitis. In the intima, where there is

calcification, are large spindle cells containing granular pigment. In some portions the pigmentation is more marked toward the adventitia and there is apparently a transition between the pigment-containing cells and those containing lime salts.

Brain. Atrophy; edema of meninges with focal thickenings. Scattered pig-

of cartilage, in many instances extending clear through. The pigmented portions of cartilage are yellowish-brown to black and in these areas the cartilage cells are necrotic with deposition of pigment in the dead cells. Only the unpigmented cartilage cells are living and here there is pigmentation of the matrix. In the lower lobes there is hypostatic congestion, early pneumonia,

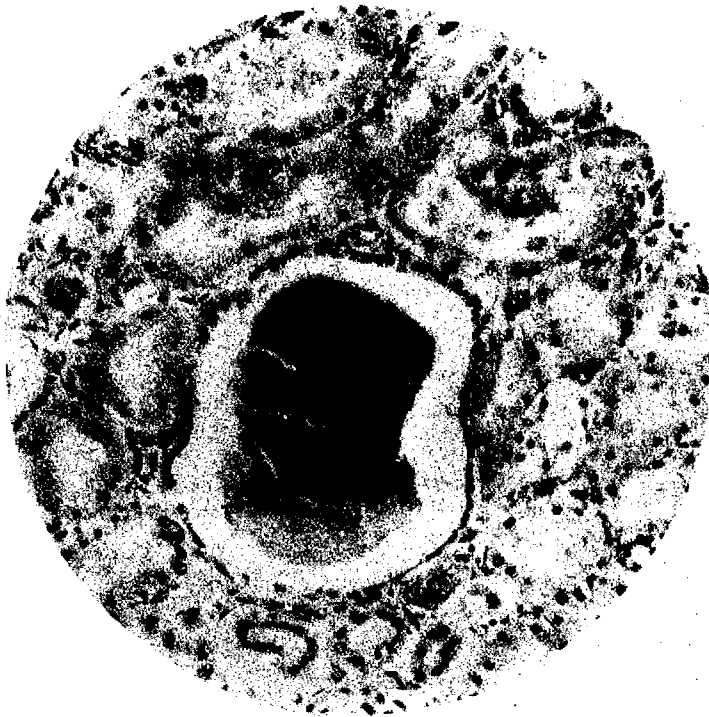


FIG. 8. DIFFUSE PIGMENT IN RENAL CAST

High power. There are many such in all kidney sections

mented cells in the pia-arachnoid. Excessive pigment in all ganglion cells. Calcification of vessels of choroid plexus with diffuse brownish pigmentation.

Dura mater. Scattered cells containing fine granular brownish pigment.

Lungs. Chronic passive congestion, emphysema, bronchiectasis. All bronchial cartilages reveal pigmentation of periphery

and catarrhal bronchitis. The pulmonary arteries are dilated, sclerotic, and show pigmented cells in the outer layers of the media. Chronic fibrous pleuritis. No tubercles found.

Trachea and main bronchi. Slight catarrh. Cartilages are pigmented in the inner layers of the perichondrium. Pigment is brown, occurring in fine granules, within

the spindle shaped cells of the perichondrium, and more marked in the perichondrium nearest the lumen. Most of the cartilage cells are unpigmented but some nearest the lumen and adjacent to the perichondrium show a slight diffuse or granular brownish tint of the cartilage capsule, but not in the cells themselves (fig. 6).

Bronchial lymph nodes. Healed and ac-

tion. Marked pigmentation of pigmented zone of the cortex. Atrophy of the medulla. No tubercles. Miliary gummata about vessels of medulla.

Kidneys. Secondary contracted kidney; arteriosclerosis with chronic parenchymatous nephritis. Several miliary gummata with giant cells in cortex. Numerous hyaline casts showing diffuse brownish pigmen-



FIG. 9. DIFFUSE PIGMENTATION OF PROSTATIC CONCRETIONS

Low power

tive tubercles in all stages; anthracosis, no other pigmentation.

Costal cartilages. Bony metaplasia of perichondrium with slight diffuse brownish pigmentation. Diffuse brownish pigmentation of the intercellular substance, most marked nearest perichondrium (fig. 7).

Left adrenal. Marked lipoidosis. Hyaline fibrosis of capsule in which there occurs slight amounts of diffuse brownish pigment. Increase of stroma with hyaline degenera-

tion (fig. 8). Some pigmented cells in connective tissue of capsule and about the vessels.

Prostate. Chronic prostatitis, still active, with multiple abscesses. Glandular hyperplasia with cystic dilatation. Varying degrees of diffuse brownish pigment in concretions. The large concretion consists of amorphous matter with dense diffuse brownish pigmentation (fig. 9).

Testes. Atrophy. Spermatogenesis present in some tubules, others show atypical spermatids. The stroma is increased and edematous; the basement membrane is thickened. Areas of orchitis fibrosa with complete hyalin degeneration of tubules. Interstitial cells hypertrophied and pigmented.

Liver. Brown atrophy. Parenchymatous degeneration. Chronic passive congestion, marked pigmented central zone. Sclerosis of arteries.

Spleen. Atrophy. Marked sclerosis of vessels, slight calcification of walls with brownish pigment in these areas. Diffuse hemoglobin in parenchyma.

Thyroid. Colloid diminished. Stroma increased. One artery shows diffuse and granular pigment in media and intima.

Pancreas. Chronic interstitial pancreatitis, syphilitic type. Diffuse brownish pigment deposits in walls of small arteries. Atrophy. Increase of stroma. Post-mortem changes.

Duodenum. Small adenomyoma in submucosa.

Gall bladder. No changes other than post-mortem necrosis.

Urinary bladder. Simple atrophy. Otherwise negative.

PATHOLOGICAL DIAGNOSIS

Ochronosis—pigmentation of skin of nose, back, scar on dorsum of left hand, costal, tracheobronchial, intervertebral and joint cartilages, endocardium, myocardium, mitral and pulmonary valves, aorta, coronary and other small arteries, bones of skull, dura mater and choroid plexus, right suprarenal gland, and prostatic concretions.

Old syphilis—syphilitic aortitis, pancreatitis, orchitis, nephritis and adrenalitis.

Complete calcification of right adrenal gland; calcification of one-half of left adrenal with atrophy and lipoidosis.

Old tuberculosis of bronchial nodes.

Parenchymatous degenerative nephritis with arteriosclerosis.

Generalized atherosclerosis.

Catarrhal bronchitis.

Terminal bronchopneumonia.

Atrophy and passive congestion of all organs.

Chronic osteoarthritis involving the vertebrae.

Chronic purulent prostatitis and vesiculitis.

Adenomyoma of duodenum.

Bilateral fibrous obliterative pleuritis.

Fibrous perisplenitis and perihepatitis.

SUMMARY OF CASE

In accord with previously reported cases of ochronosis there is pigmentation of the structures most frequently found involved; costal, tracheobronchial, sternoclavicular and intervertebral cartilages, and skin. Pigment is also found in all of the widely distributed areas of degeneration or necrosis, atherosclerotic plaques, areas of calcification, scars, renal casts and prostatic concretions. In addition pigment occurs in places less commonly found in ochronosis, such as the bones of the cranium and ribs, and also in the dura mater. The pigment is both granular and diffuse, intra- and extracellular. In cartilage it is deposited only in the matrix and to a slight degree in the cartilage capsule. Dead cells are deeply pigmented. The pigment must have been excreted in the urine since it is abundant in the numerous renal casts.

Chronic arthritis involving the vertebrae and cardiovascular changes in the form of generalized atherosclerosis are present. Both chronic arthritis and cardiovascular changes have frequently been found accompanying ochronosis.

The age of the patient, eighty-five, is greater than that of any previously reported case.

Further interest is added by the presence of almost complete destruction of the adrenal glands, due to

syphilis, suggesting that this may be the cause or one of the causes of the ochronosis. At least, the presence of two distinct conditions either of which may cause pigmentation of the skin is unusual and interesting.

Accurate classification of the case is not possible because of the meager history and the failure to examine

the urine. Whether there was an accompanying alcaptonuria or melanuria is not known. There is no history of the prolonged external use of phenol. The case then belongs either in the group of cases in which the ochronosis is due to alcaptonuria or those cases of ochronosis with melanuria.

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