A RARE CASE OF ALKAPTONURIA: CASE REPORT

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ABSTRACT

INTRODUCTION

Alkaptonuria is a rare metabolic autosomal recessive disorder due to Homogentisic acid oxidase deficiency. There is generalized deposition of oxidized HGA in tissues mainly in fibrous and cartilaginous tissues. The disease is generally characterized by dark urine, ochronosis, and arthritis. A 50-year-old female attended the hospital with severe Joint Pain, Itching, Parasitophobia, Difficulty in hearing, Lack of clear vision and Discoloration of urine for different durations ranging from 6 months to 10 years. Alkaptonuria was suspected and accordingly detailed clinical examination and investigations were carried out. Biochemical analysis was positive for Alkaptonuria, X-ray was supportive for the diagnosis, and Histopathological examination revealed alkaptonuric pathology. The treatment was initiated with Ascorbic acid and protein restricted diet with symptomatic management and being followed up.

KEYWORDS

Alkaptonuria, Homogentisic Acid Oxidase, Ochronosis, Arthritis.

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INTRODUCTION: Alkaptonuria is a rare metabolic autosomal recessive disorder with an incidence of 1 in 250000.[1] Alkaptonuria is due HGA oxidase deficiency. The defective gene is located in long arm of chromosome 3 and several disease causing mutations were identified.[2] The Phenylalanine and tyrosine catabolism is blocked at HGA level and HGA excretion is 10 times the normal. Large quantities of HGA is excreted in the urine, which turns dark on standing.[3] In urine as in tissues, HGA oxidizes to benzoquinones, which in turn form melanin-like polymers. Accumulation of HGA and its metabolites in tissues causes ochronosis with darkening of cartilaginous tissues and bone, arthritis and joint destruction and deterioration of cardiac valves.[3,4,5] There is generalized deposition of oxidized HGA in tissues mainly in fibrous and cartilaginous tissues.

This case of Alkaptonuria is presented for its rarity of occurrence and as it is not often reported. A 50-year-old female residing in Walaja, Vellore District, Tamil Nadu, India, came to the hospital with severe Joint Pain, Itching, parasitophobia, difficulty in hearing, lack of clear vision and discoloration of urine for different durations ranging from 6 months to 10 years. Alkaptonuria was suspected and accordingly detailed clinical examination and investigations were carried out.

MATERIALS AND METHODS: We elicited a detailed case history including family history. We conducted a detailed clinical examination of the patient as well as their family members. We conducted urine examination, complete hemogram, blood urea, serum creatinine, Benedict's test, ferric chloride test, radiological imaging of the vertebra and histopathological examination for confirmation of diagnosis.

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CASE PRESENTATION: The patient came to treatment for the cure of itching and parasitophobia for the past 2 months. On elicitation of history she was found to have suffered from different symptoms. She has been suffering from severe joint pains for the past 2 years. The small and large joints of both upper limb and lower limb are involved. Also she has pain in Axial Joints. She has been passing dark discoloured urine since the age of 10 years. Palms and finger tips are darkly discoloured for the past 8 years. Further for the past 1 year she has difficulty in vision and in hearing.

The patient is a first born child to first degree consanguineous parents. She has one younger brother and a younger sister. Both are Normal. Patient was married to her maternal uncle and has 2 daughters and one son. They are normal. Her first daughter is married to maternal uncle (Patient's brother) and has two grand-daughters. The first grand daughter who is 7 years old gives history of dark discolouration of urine. Her second grand-daughter is suffering from Autism. Patient's second daughter is married but not consanguineous and has 2 children who are normal. Her son is not yet married. With these clinical findings investigations were carried out.

RESULTS: The results are presented as follows. The history suggestive of Alkaptonuria are severe joint pains small and large joints in both upper and lower limbs, pain in axial joints, dark discolouration of urine, discolouration of palms and finger tips, difficulty in vision and hearing. The general examination revealed bluish black pigmentation of the skin over the hypothenar and thenar area in both the palms and also in the finger tips.

On examination of the Ear, Pigmentation was observed in concha and outer rim of both the ears. ENT opinion was sought for. A rim of pigmentation was seen on the tympanic membranes. Throat, nose, oral cavity and Vocal cords were normal. Audiogram was Normal. There was no conductive deafness.

Ophthalmologist confirmed the presence of ring shaped pigmentation in the right sclera in the pericorneal area. Slit Lamp Examination showed Pigmentation over the anterior capsule of the right lens.

Hemogram was normal. Urea Creatinine was normal. Biochemical analysis of urine for Alkaptonuria such as Benedict's test, Ferric chloride test were positive, urine on standing with addition of sodium hydroxide showed a dark ring.

X-ray revealed intervertebral disc calcification. Histopathological section showed Fragmentation and fracture of collagen bundles.

DISCUSSION: The disease is generally characterized by dark urine, ochronosis, and arthritis. The characteristic symptoms in childhood are dark urine, staining of napkins and under clothes. Ochronosis used to describe the darkening of tissue to slow accumulation of the black polymer of Homogentisic acid in cartilage and other mesenchymal tissue, which is seen in the 4th decade of life. Pinna is flexible initially and gradually calcified later. The cerumen may appear jet black. Deafness can occur due to deposition in the ear ossicles. Ocular pigmentation occurs in about 70% of the patients.[6] The brown grey deposits in the sclera is named as Osler's sign which is usually evident in the 3rd decade of life.[7] Dusky cutaneous deposit occurs in the cheek, axillae and Genitals. And also occur in the buccal mucosa, in the nails leading to nail changes. Arthropathy usually occurs in the 5th decade of life mainly affecting the large joints such as knees, shoulders and hip but generally initial manifestation as Lumbar spondylosis. Patient presents with low back ache and stiffness resembling the rheumatoid arthritis with radiological finding resembling osteoarthritis.[8] Intervertebral disc prolapse occurs due to friable articular cartilage leading to clinical presentation of loss of height and stooping posture.

Calcium pyrophosphate crystals and pigment fragments may be in synovial fluid.

Pigment deposits can be intracellular may involve internal organs such as great vessels, valves of Heart, Endocardium, Kidney, Oesophagus, tonsil, Dura Mater, etc.[9] The diagnosis is confirmed by measurement of homogentisic acid in urine. Affected patients may excrete as much as 4 to 8gm of this compound daily. The inability to convert homogentisic acid to maleyl acetoacedic acid results in accumulation of homogentisic acid and a product of its oxidation, benzoquinone, which induces tissue injury. Homogentisic acid is a strong reducing agent that produces a positive reaction with Fehling's or Benedict's reagent, but not with glucose oxidase. The enzyme is produced only in the liver and kidney.

Our case patient presented with classical features of arthropathy, dark discolouration of urine, ear involvement which strongly suggested a clinical suspicion of Alkaptonuria. In addition the family history strongly supported the suspicion.

The diagnosis of alkaptonuria should be supported by demonstration of HGA in Urine and confirmed by Histopathological examination, Specific enzyme test, Gas liquid chromatography.

HPE with Eosin stains the ochronotic pigment yellow. Pigments are deposited as fine granules causing homogenization and swelling of the collagen bundles. Collagen bundles become rigid and break up. These are seen as free yellow pigments lying freely in the tissues along with giant cell response. The pigments are differentiated from melanin pigment in that they are not stained by silver nitrate. Similarly this pigments stains black with cresyl violet staining. In addition brown black pigments are found in cartilage, fibrous tissue, tendons, intervertebral discs, larynx and tracheal rings.

The diagnosis in our case was made on the basis of the presence of the triad of ochronotic pigmentation of the sclera, urine which turns black upon alkalization and detection of homogentisic acid in the urine. The diagnosis was supported by Histopathological Examination.

The differential diagnoses are Addison's disease, Hemochromatosis, Photosensitive pigments, porphyria, and Pellagra. Another entity called acquired ochronosis may mimic Alkaptonuria.[10] Addison's disease is characterized by existing pigments, mucosal, nail changes. Hemochromatosis may present with Grey brown pigment and complications such as Bronze Diabetes Mellitus, Cirrhosis, etc. Acquired ochronosis may result due to sulphydryl group HGA oxidase, inhibited by certain chemicals and drugs, phenol, resorcin, mepacrine picric acid, HQ containing bleaching creams.

There is no specific treatment for Alkaptonuria. Specific restriction of tyrosine and phenylalanine or low protein diet is to be advocated. Arthritis has to be managed symptomatically. Ascorbic acid may be helpful as it blocks inhibition of Lysyl Hydroxylase activity.[11,12,13] Use of Nitisonine, a drug used in Tyrosinemia Type I, reduces the urinary excretion of HGA by inhibiting homogentisic acid production* and thereby preventing the long term complications of Alkaptonuria.[12] Treatment with vitamin C to enhance HGA degradation has not proved helpful.[3,8] However, 2-(2-nitro-4-trifluoromethyl benzoyl) -1,3-cyclohexanedione, or nitisinone (Orfadin), has been proposed as potential therapy.[10] because it inhibits the enzyme that produces HGA, i.e. 4-hydroxyphenylpyruvate dioxygenase. Several therapeutic approaches have been used in patients with alkaptonuria. High-dose vitamin C decreases urinary benzoquinone acetic acid but has no effect on HGA excretion.[8] and no credible studies have shown that treatment with vitamin C is clinically effective.[12] 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione, or nitisinone (Orfadin), has been proposed as potential therapy[9] because it inhibits the enzyme that produces HGA i.e., 4-hydroxyphenylpyruvate dioxygenase. Our patient was managed with Vitamin C, Protein restriction and Physiotherapy for joint symptoms. The patient is being followed up and symptomatic management is continued.

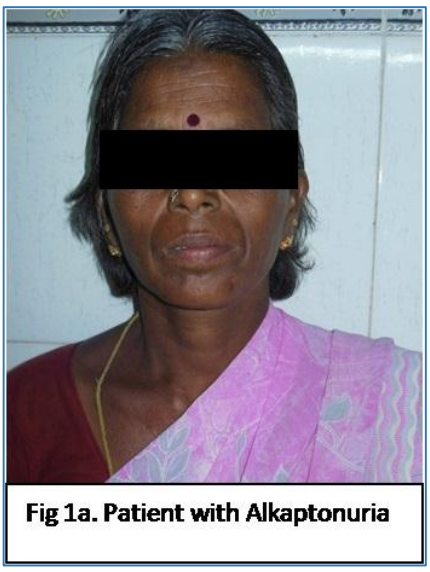

Fig 1a. Patient with Alkaptonuria

Fig. 1b Patient and her grand daughter affected with Alkaptonuria

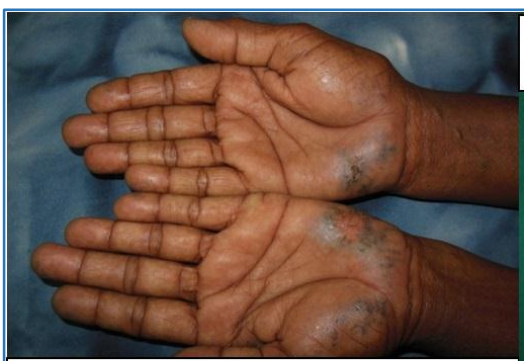

Fig 2a. Bluish Black pigmentation over thenar and Hypothenar spaces of both palms

Fig 2b. Bluish Black pigmentation seen over Finger tips of both hands

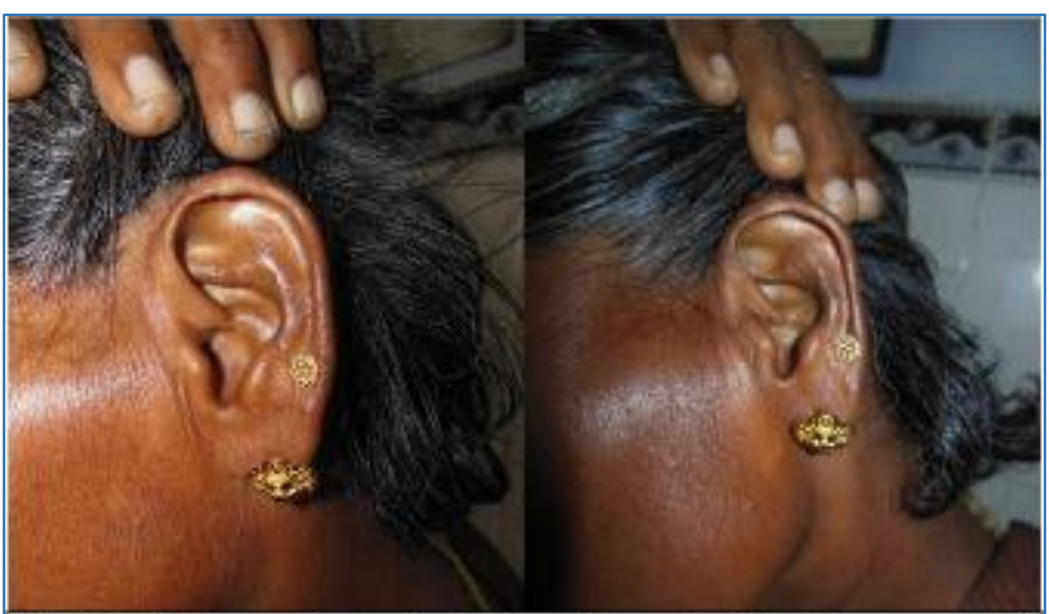

Fig 3a. &3b. Pigmentation in the Concha and outer rim of the Left ear

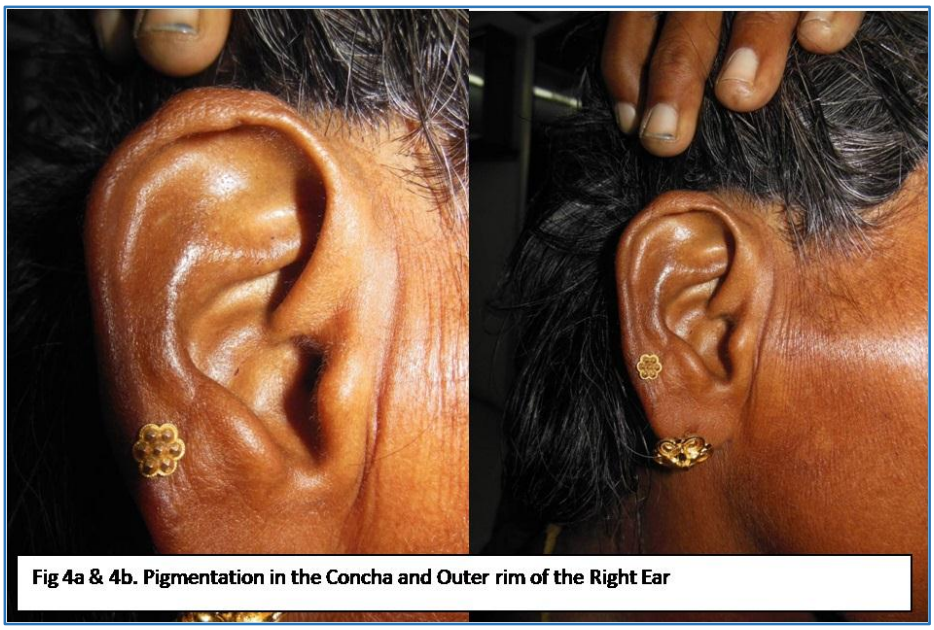

Fig 4a & 4b. Pigmentation in the Concha and Outer rim of the Right Ear

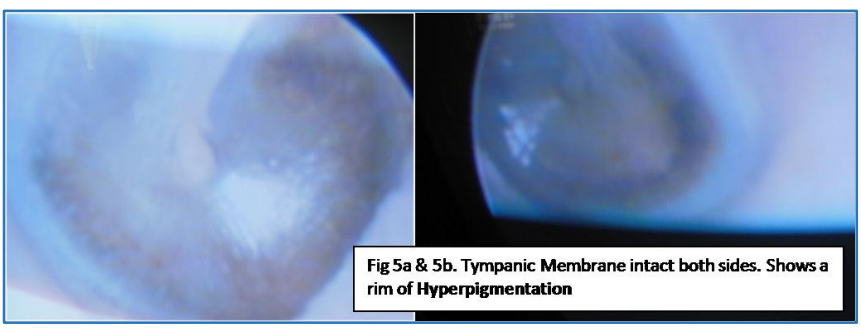

Fig 5a & 5b. Tympanic Membrane intact both sides. Shows a rim of **Hyperpigmentation**

Fig 6. Pigmentation over Right Sclera

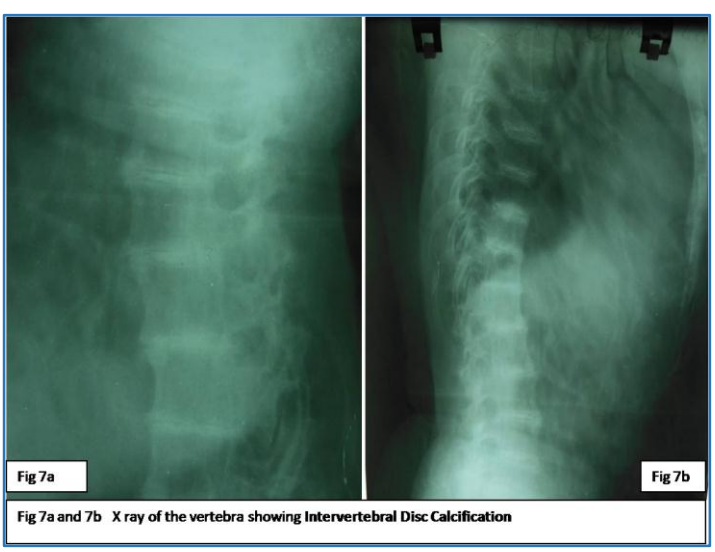

Fig 7a

Fig 7b

Fig 7a and 7b X ray of the vertebra showing **Intervertebral Disc Calcification**

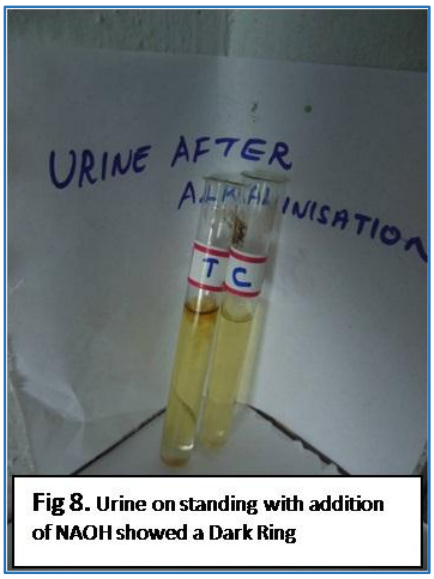

Fig 8. Urine on standing with addition of NAOH showed a Dark Ring

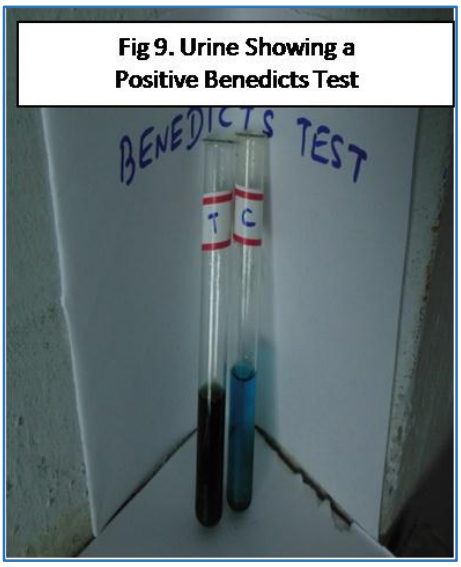

Fig 9. Urine Showing a Positive Benedicts Test

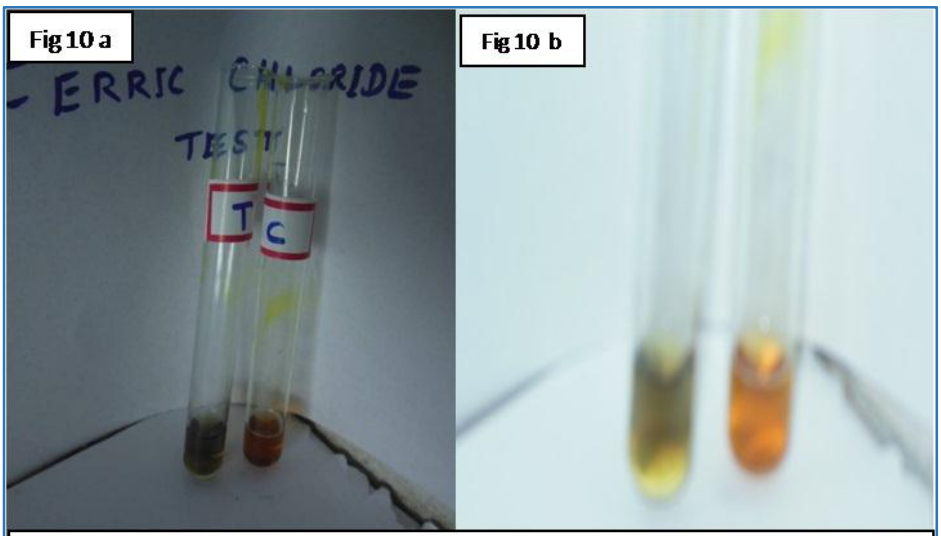

Fig 10 a . Showing Positive Ferric Chloride Test **Fig 10 b.** Closer View

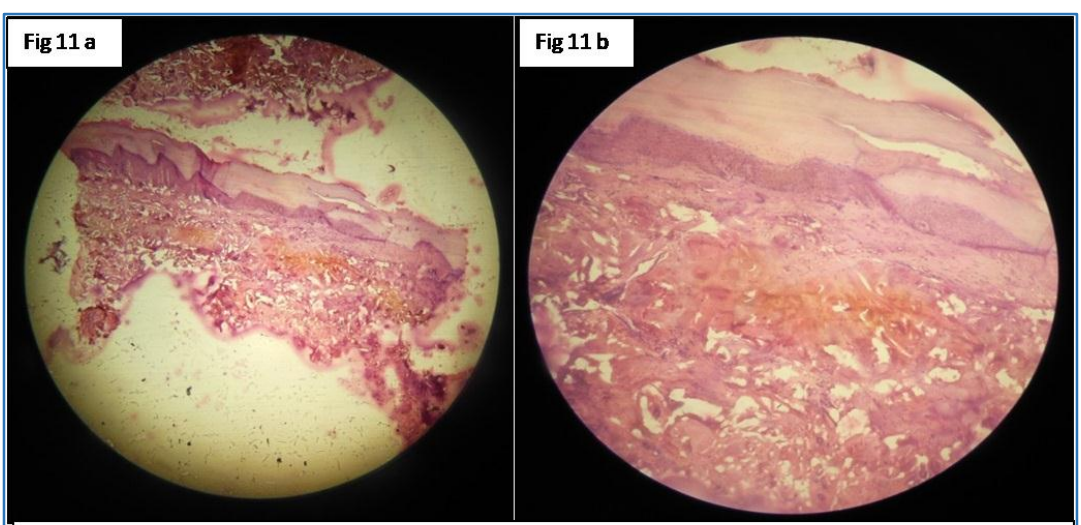

Fig 11 a .(H&E X100) Yellow Brown pigmentation of Dermal Collagen Bundles. Scattered Lymphocyte infiltration of Upper Dermis. **Fig 11 b.** (H&E X 400) Brown pigmentation of Dermal Collagen Bundle. Scattered Lymphocyte infiltration in Upper Dermis

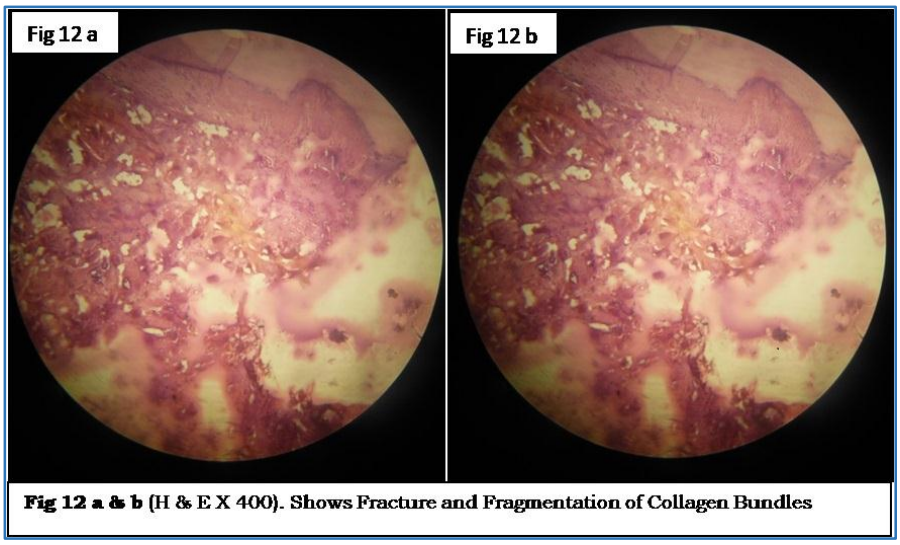

Fig 12 a & b (H & E X 400). Shows Fracture and Fragmentation of Collagen Bundles

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