Cerebrotendinous Xanthomatosis Unmasked by Cutaneous Xanthogranuloma: A Clinicopathological Case Report: A Rare Case Report

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Abstract: ***Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive lipid storage disorder caused by defective bile acid synthesis, leading to accumulation of cholestanol in multiple tissues. We report a case of a 29-year-old male with intellectual disability and long-standing seizures who presented with multiple painless tendon and cutaneous swellings. Histopathological examination of an excised cutaneous nodule revealed sheets of foamy macrophages, Touton-type giant cells, and cholesterol clefts, suggestive of xanthogranulomatous pathology. Subsequent clinicoradiological correlation demonstrated diffuse cerebral and cerebellar atrophy with chronic white-matter ischemic changes on MRI, along with a history of juvenile cataract, delayed milestones, neonatal jaundice, and chronic diarrhea. Routine lipid profile was within normal limits, excluding common hyperlipidemic xanthomatoses. Based on the characteristic clinical, radiological, and histopathological features, a diagnosis of cerebrotendinous xanthomatosis was established. This case highlights the critical role of pathological vigilance and multidisciplinary evaluation in diagnosing this rare yet treatable metabolic disorder.***

Keywords: Cerebrotendinous xanthomatosis, tendon xanthoma, foamy macrophages, Touton giant cells

1.Introduction

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive inborn error of bile acid metabolism resulting from mutations in the *CYP27A1* gene, which encodes sterol 27-hydroxylase. The enzymatic defect leads to reduced synthesis of primary bile acids, particularly chenodeoxycholic acid, causing accumulation of cholestanol and bile alcohols in various tissues. Clinically, CTX is characterized by progressive neurological dysfunction, intellectual disability, juvenile cataracts, tendon and cutaneous xanthomas, and multisystem involvement.

Due to its rarity and nonspecific early manifestations, CTX is frequently underdiagnosed or misdiagnosed, often leading to irreversible neurological damage before appropriate treatment is initiated. Recognition of characteristic histopathological findings in skin or tendon lesions may provide a crucial diagnostic clue. We present a case of CTX diagnosed through clinicopathological correlation following evaluation of a cutaneous xanthogranulomatous lesion.

2.Case Report

A 29-year-old male presented with multiple swellings over the trunk, Achilles tendon, extensor tendons of the elbow and hands. The swellings were firm, non-tender, and fixed to underlying structures. The patient had a history of intellectual disability, delayed developmental milestones, and recurrent seizures since childhood, for which he was on carbamazepine therapy. There was no significant family history.

Further clinical evaluation revealed a history of neonatal jaundice, chronic diarrhea during infancy, and bilateral cataract surgery performed at the age of 15 years. Ophthalmologic examination at presentation did not reveal Lisch nodules.

Routine hematological and biochemical parameters were within normal limits.

Magnetic Resonance Imaging (MRI) of the brain demonstrated diffuse cerebral and cerebellar atrophy along with bilateral, symmetrical hyperintense signal changes in the periventricular and deep white matter on T2-weighted and FLAIR sequences, consistent with chronic white-matter ischemic changes.

Histopathological Findings:

Microscopic examination revealed skin lined by epidermis with focal ulceration Dermis shows chronic inflammatory infiltrate predominantly composed of sheets of multiple foamy macrophages (xanthoma cells), touton type giant cells characterized by vacuolated cytoplasm and ring like arrangement of nucleus and cholesterol clefts consistent with cutaneous xanthogranulomatosis.

An excised nodular lesion with attached skin from the right knee measured 5 × 4.5 cm, with a focally ulcerated area measuring 2 × 1 cm. The initial diagnosis mentioned on the requisition form was neurofibroma.

Diagnosis:

Based on the characteristic clinical and radiological early-onset neurological involvement, intellectual disability, tendon xanthomas, delayed milestones, young age cataract, multiple tendon and cutaneous swelling, history of neonatal jaundice, diarrhoea and confirmatory histomorphology, a diagnosis of cerebrotendinous xanthomatosis was made. Early recognition of CTX is crucial, as timely initiation of chenodeoxycholic acid therapy can halt disease progression and prevent irreversible neurological damage.

Clinical Images

Microscopic Images

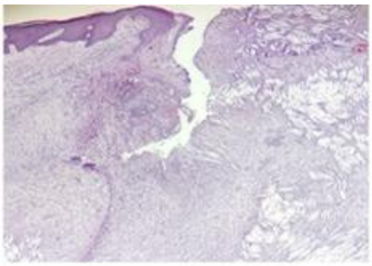

Figure 1

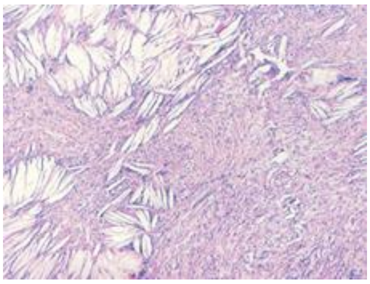

Figure 2

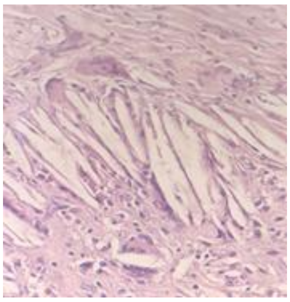

Figure 3

Figure 1-Low-power photomicrograph (scanner view) showing skin with epidermis displaying focal **ulceration**. The underlying dermis shows a diffuse xanthogranulomatous infiltrate. **Figure2**-Medium-power photomicrograph showing sheets of foamy macrophages (xanthoma cells) with abundant vacuolated cytoplasm and cholesterol clefts within the dermis. **Figure3**-High-power photomicrograph highlighting **Touton-type giant cells**, along with adjacent foamy macrophages and cholesterol clefts.

3.Discussion

Cerebrotendinous xanthomatosis is a progressive lipid storage disorder resulting from sterol 27-hydroxylase deficiency, leading to impaired bile acid synthesis and accumulation of cholestanol in lipid-rich tissues such as the brain, tendons, and skin. The disease typically manifests in infancy or childhood with nonspecific gastrointestinal symptoms, followed by juvenile cataracts, neurological deterioration, and tendon xanthomas in early adulthood.

In the present case, the constellation of intellectual disability, seizures, juvenile cataracts, tendon and cutaneous xanthomas, and characteristic neuroimaging findings strongly supported the diagnosis of CTX. Importantly, the patient had a **normal lipid profile**, a hallmark feature that differentiates CTX from familial hypercholesterolemia and other hyperlipidemic xanthomatoses. The absence of neurofibromatosis-related tumors on imaging and lack of Lisch nodules further excluded the initial clinical suspicion of neurofibroma.

Histopathological identification of foamy macrophages, Touton giant cells, and cholesterol clefts was pivotal in raising suspicion of a systemic lipid storage disorder. Although biochemical confirmation by serum cholestanol estimation and genetic testing for *CYP27A1* mutation is ideal, these investigations may not be readily available in resource-limited settings. In such scenarios, a combination of clinical, radiological, and pathological findings is sufficient to establish a diagnosis.

4.Conclusion

This case emphasizes that **cerebrotendinous xanthomatosis should be suspected in young patients presenting with tendon or cutaneous xanthomas, seizures, intellectual disability, juvenile cataracts, and normal serum lipid profiles**. Histopathological identification of foamy macrophages, Touton giant cells, and cholesterol clefts plays a decisive role in triggering further clinicoradiological evaluation and literature review, especially in settings where advanced biochemical and genetic tests are unavailable. Early recognition of this rare yet treatable disorder is essential, as timely initiation of CDCA therapy can significantly alter disease course and prevent progressive neurological deterioration

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