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Case Report

Cholesterotic fibrous histiocytoma (CFH): A case report

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Abstract

An elderly male patient complained of a small nodule, measuring 0.3 cm³ in right upper eye-lid. Microscopically, it showed chronic inflammation. Aggregates of cholesterol crystals were seen. Several multinucleate giant cells were also seen. The patient had persistently raised hyperlipoproteinemia which might hasten the progression of cholesterotic fibrous histiocytoma. Overlying squamous epithelium showed acanthosis, hyperkeratosis and papillary processes. He was finally diagnosed as a case of cholesterotic fibrous histiocytoma (CFH).

Keywords: Cholesterol-induced inflammation, Giant cells and macrophages, Fibroblastic proliferation, Acanthosis, Hyperkeratosis.

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1. Introduction

Hunt et al reported a case CFH in the year1990 [1]. She had two lesions which involved left leg and right thigh. Left leg lesion showed features of a fibrous histiocytoma and right thigh lesion showed abundant cholesterol clefts. Current patient was an elderly male and he had poorly-controlled hyperlipoproteinemia for the last 7 years.[1] He developed a nodule in right upper eye-lid for the last 3 years which was surgically excised. Microscopically, it showed subepithelial dermal tissue with chronic granulomatous inflammation. In addition, large number of cholesterol crystals were also seen. Later, in another patient,[2] multiple eruptive papules, consisting of histiocytes and fibroblasts were detected along with cholesterol clefts in the year 2021. Similar lesion was also detected by Lukach et al.[3] Present lesion was extremely rare. Only 3 definitive cases of CFH with hyperlipoproteinemia have been reported earlier in English literature before the year 2015.[4] Subsequently, another single case was described where a nodule with similar histopathological features was described in a 50-year-old patient.[4] Hyperlipoproteinemia was suspected to have a role in etiopathogenesis of CFH.[4] In addition, rabbits given cholesterol-rich diet developed multiple xanthomas.[4] Electron microscopic findings in CFH might show cholesterol crystals in the cytoplasm and lipid droplets in the lysosomes of histiocytes.[2] Multiple xanthomas have been shown to develop in LDL receptor negative (LDLR-/-) cholesterol-fed mice.[5] Moreover, uptake of LDL by monocytes may result in formation of foam cells.[4] The present case was reported in the year 2025.

2. Case Report

A 59-year old female patient complained of a nodule in right upper eye-lid for the last 3 years. It measured 0.3 cm³. Later, the nodule was excised. Microscopically, the lesion comprised of large number of small lymphocytes, few plasma cells and several multinucleate foreign body giant cells along with cholesterol clefts (**Figure 1**A). Diffuse lymphocytic infiltration was seen (**Figure 1**B). Lesion was well-circumscribed showing dense fibrosis and hyalinization (**Figure 1**C). Large number of cholesterol crystals and few

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giant cells were also seen (**Figure 1**D). Serum total cholesterol was in normal reference range due to its deposition in stromal tissue. **Figure 1**E showed large number of fibroblasts and histiocytes (Masson trichrome ×100). Immunohistochemistry (IHC) examination showed strong positivity (3+) of macrophages and giant cells with anti-CD68 antibody (**Figure 1**F). Anti-CD34 antibody stained endothelial cells (**Figure 1**G). Inflammed tissue was partially covered with hyperkeratinized squamous epithelium with papillary processes.

Serum total cholesterol was 88 mg/dl (reference range <220 mg/ dl). Serum lipoproteins were raised (252mg/dl), suggesting hyperlipoproteinemia (reference range < 75 mg/dl). Other lipid parameters were within normal range.

3. Discussion

Most important feature of present case was the presence of chronic inflammation in the sub-conjunctival compartment of right upper eye-lid. It consisted of a dermal-based fibroblastic proliferation. Large number of histiocytes with fair number of multinucleate giant cells were seen. Thick fibrosis and hyalinization were also seen (**Figure 1**E). In addition, large number of cholesterol crystals/clefts were seen both extracellularly as well as inside the giant cells, suggesting their etiological role (**Figure 1**D). Association with hyperlipoproteinemia along with chronic inflammation suggested the etiological role of low density lipoproteins in pathogenesis of CFH.[5] CFH may be a rare variant of dermatofibroma.[6] Clinically, it may resemble with malignant melanoma. Moreover, appearance of the current lesion suggested possibility of a metabolic disorder.[4] Which could not be explained. However, it was suggested that CFH might be a lesion associated with histiocytic appearance which was expressed in the microenvironment of hyperlipoproteinemia.[6] Moreover, epithelium showed acanthosis, hyperkeratosis with papillary processes. An earlier patient had both hypertriglyceridemia as well as hyperlipoproteinemia.[4] Phagocytic activity of fibrous histiocytes was earlier reported by Senear and Caro.[7] Etiopathogenesis of CFH is not clearly understood.[4] In another study, 3 of 5 children had hyperlipidemia at younger age and later one of them died of acute myocardial infarction at the age of 33 years.[1] It was reported by Hunt et al.[1] Masson trichrome stained the collagen (**Figure 1**E). IHC examination showed strong positivity of histiocytes and giant cells with anti- CD 68 antibody (**Figure 1**F). Anti-CD 34 antibody stained fair number of endothelial cells (**Figure 1**G). Xanthomas are known to develop in patients with hyperlipoproteinemia associated with metabolic syndrome.[4,8,9] Xanthomas may occur following minor trauma to skin, leading to vascular leakage of cholesterol, followed by phagocytosis.[9,10]

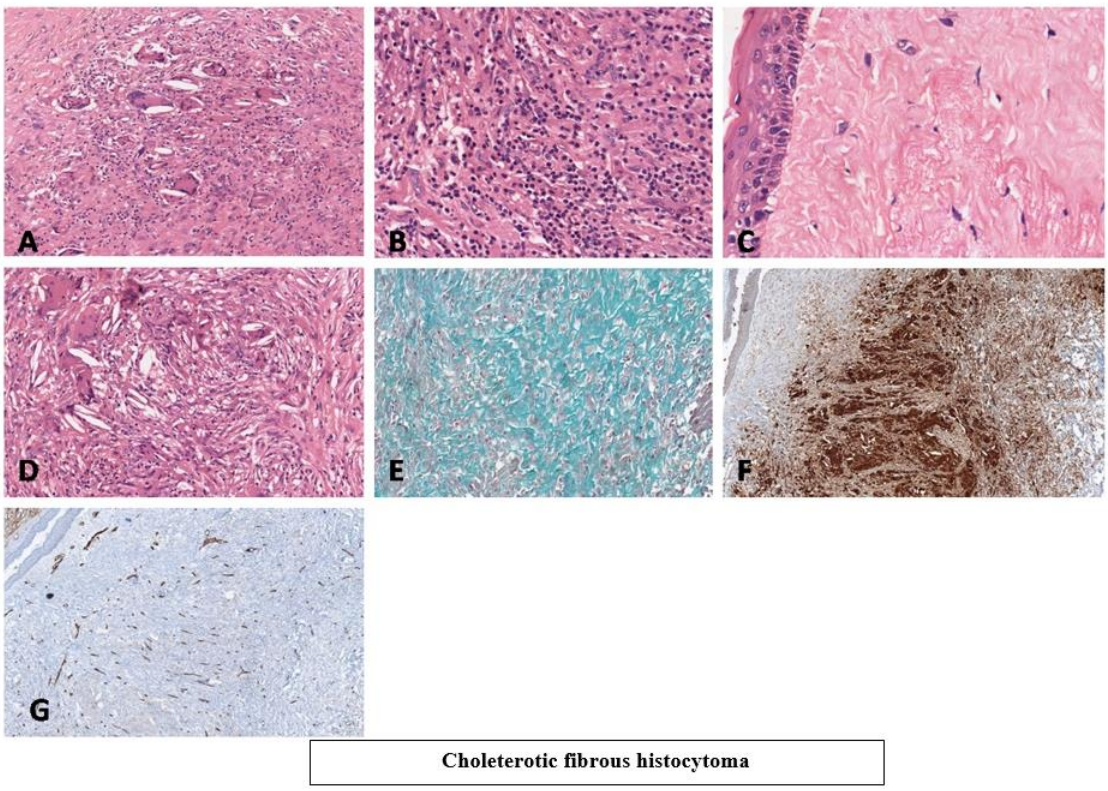

Figure 1: (A) Photomicrograph showed several giant cells. Cholesterol clefts were seen. Background contained lymphocytes (HE×100). **(B)** Focal collections of large number of lymphocytes were seen (HE×400). **(C)** Photomicrograph showed hyalinized bundles of collagen fibers and few spindle cells (HE×400). **(D)** Showed large number of cholesterol crystals as clefts (HE×100). **(E)** Showed large number of fibroblasts and collagen (Masson trichrome×100). **(F)** Immunohistochemistry showed strong positivity of histiocytes and giant cells with anti-CD 68 antibody (×100). **(G)** Anti-CD 34 antibody stained fair number of endothelial cells (× 100)

In an experimental study, LDL receptor negative -/- mice fed on cholesterol-rich diet, developed both hypercholesterolemia as well as xanthomas. On the contrary, ApoE deficient -/- mice fed on cholesterol-rich diet developed hypercholesterolemia alone without developing xanthomas. Results of cholesterol-rich diet suggested the role of multiple genes in pathogenesis of xanthomas.[5] Xanthomatosis might be accelerated by action of Apo-E gene. Apo-E protein may be an agent for lipoprotein uptake by macrophages.[11] Most common differential diagnosis may be a variant of dermatofibroma (DF). DF is characterized by epidermal alterations and dermal changes.[12] Commonest variant of DF may be fibrocollagenous. Another subtype may be histiocytic variant. lipidized fibrous histiocytoma is comprised of foamy macrophages and collagenous bundles.[13] CFH appears to be a rare variant of DF.[14]

Salient features of previously reported cases of CFH are given in **Table 1**. As it will appear, CFH is associated with epithelial as well as stromal changes. Epithelial changes showed acanthosis, hyperkeratosis and papillary process while stromal changes showed chronic granulomatous inflammation and cholesterol crystals.

Table 1: Clinicopathological features of previously published cases of cholesterotic fibrous histiocytoma in comparison to present case

Case. No	Authors	Age (Years)	Gender	Gross findings	Microscopic features	Remarks
1	Hunt S J et al.[1]	63	Female	Patient had nodular lesions. Size of lesions measured 1 cm and 1.4 cm in leg and thigh.	Right thigh lesion showed cholesterol aggregates in center of nodule. Left leg lesion showed fibrosis and hyperpigmentation of basaloid epithelial cells.	Patient had 5 children. One of them died at the age of 33yrs. Serum triglycerides and S.LDL were slightly raised
2	Yu M, et al.[15]	39	Male	Patient had brownish papule in axilla of right thigh.	Cholesterol aggregates in central nodular area were detected. In addition, epidermal changes as Acanthosis, basal cell changes were seen. ill-defined dermal lesion was seen.	Leakage of lipoproteins was followed by cholesterol cleft formation.
3	Dhar S, et al.[2]	15	Male	Lesion was present on right thigh.	Hyperpigmentation of basal layer and elongation of rete ridges, separated by clear Grenz zone, were found.	Features of both histiocytic and fibroblastic differentiation were seen.
4	Deguchi M, et al.[4]	50	Male		Hyperkeratotic nodule 0.6 cm. Lesion was present on left lower extremity. Tumor was composed of fibroblasts and CD68+ cells, negative for CD34 cells. Numerous factor XII a-positive cells may be detected.	Both metabolic syndrome and hyperlipoproteinemia may be responsible for the lesion.
5	Present patient	59	Female	Nodular lesion at right upper eye- lid (size 0.3 cm)3.	Section showed large number of macrophages, admixed with lymphocytes and several giant cells. Lesion was well circumscribed with fibrosis.	Patient had hyperlipoproteinemia (S. lipoproteins (252 mg/dl) Reference range (<75 mg/dl).

4. Conclusion

An elderly patient complained of a nodule in sub-conjunctival compartment. Microscopically, it showed large number of lymphocytes, fibroblasts, histiocytes and foreign body giant cells. Anti-CD 68 antibody stained both histiocytes and giant cells. Lesion appeared to be a cholesterotic variant of dermatofibroma. Current lesion also showed changes in squamous epithelium in the form of acanthosis and papillary processes. Finally, the lesion was diagnosed as cholesterotic fibrous histiocytoma. Gene therapy may be beneficial for patients with familial hypercholesterolemia.

5. Source of Funding

None.

6. Conflict of Interest

None.

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