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Xanthoma

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Introduction

Xanthomas are localized lipid deposits within an organ system. Although innately benign, they are often an important visible sign of systemic diseases. These lesions were initially described in the early 1900s, along with reports of their association with lipid metabolism.[1]

As a clinical entity, the relevance of xanthomas extends to multiple disciplines, including general medicine, pediatrics, dermatology, and surgery. Their pathophysiology and management have generated much interest in current literature. They can involve essentially all anatomical regions and organ systems of the human body, but they tend to show predilection towards the skin and subcutaneous tissue. The natural history and patterns of spread of these lesions are closely associated with that of the specific underlying systemic disease which is responsible for their existence.

Etiology

Not all patients with hyperlipidemia or hypercholesterolemia develop xanthomas. However, the presence of xanthomatous lesions can serve as a unique and important clinical indicator of these metabolic states.[2] In patients with hyperlipidemia, circulating lipoproteins permeate between vascular endothelial cells to get deposited in the dermis, subcutaneous tissues, and tendons. Phagocytosis by the tissue macrophages then helps remove the lipid components of these deposits from those sites. This mechanism is reported to be the origin of the characteristic "foam cells" found in xanthomas.[3]

Normocholesterolemic xanthomatosis is postulated to occur through an alternate sequence of events in which local tissue injury (either through trauma or inflammation) is thought to play a major role. These are the typical "eruptive xanthomas" associated with the type I, IV and V classes of hypercholesterolemias. The increased vascular permeability induced by the injury state is hypothesized to lead to the same common pathway of leaked lipoproteins that are then phagocytosed by dermal cells.[4] This pathway has been hypothesized as the etiology for lesions that are found in areas that undergo frequent mechanical trauma such as xanthomas of the Achilles tendon, which is typically seen in the type II class of hypercholesterolemia.[5]

Xanthomatous lesions are also rarely associated with paraproteinemias, including those with normal levels of plasma lipids. In these patients, it is postulated that the typically grouped, flat lesions represent the cutaneous proliferation of lymphoreticular tissue that then subsequently develops xanthomatous characteristics.[6] Cerebrotendinous xanthomatosis represents yet another separate normolipidemic clinical entity wherein xanthomas are found in the brain and various extremity tendons in the setting of elevated blood cholesterol. This disease state is associated with a genetic mutation of CYP27A1 and is an autosomal recessive lipid disorder.[7]

Epidemiology

Although xanthomas can appear at any age, they typically tend to appear in the second decade of patients with predisposing systemic conditions such as familial hypercholesterolemia.[2] Approximately 75% of geriatric patients with familial hypercholesterolemia have been shown to have a tendinous xanthoma.[8] In a large retrospective study of 5504 benign cutaneous neoplasms of eyelids seen in a Swiss ophthalmology department, approximately 6% were xanthelasmas.[9] As xanthomas are often associated with various systemic diseases, the prevalence of these lesions is inherently linked to the prevalence of these conditions.

Pathophysiology

The pathophysiology of xanthomas is a result of the metabolic breakdown of lipoproteins. Once absorbed into the circulation, very-low-density lipoprotein (VLDL) in the adipose and muscle tissue requires lipoprotein lipase (LPL) to cleave it to extract triglycerides forming intermediate-density lipoprotein (IDL) that is made up of apoprotein B-100 and apoprotein E. IDL can be resorbed into the liver via the low-density lipoprotein (LDL) receptor or converted into apoprotein B-100. However, alterations in the lipoproteins via genetic mutations result in defective apolipoproteins that yield hypolipoproteinemia or hypercholesterolemia seen visibly as xanthomas, or other systemic metabolic diseases such as diabetes mellitus, hypothyroidism, or nephrotic syndromes.

The classification of the various hypercholesterolemias based on this is beyond the scope of this summary, but various xanthomas predominantly correlate with different subtypes of hypercholesterolemias.

History and Physical

Patients with cutaneous or tendinous xanthomas often present to their primary care clinician or a variety of specialty providers including dermatology, general surgery, orthopedic surgery, and ophthalmology. It is not uncommon for these patients to present to specialty clinics for the treatment of a visible lesion and then be diagnosed with an associated metabolic condition such as familial hypercholesterolemia. Therefore, providers of various disciplines must be familiar with the presentations of these fairly common lesions and their associations with systemic disease.

On clinical exam, xanthomas have been generally described as lesions that are eruptive, tuberoeruptive, tuberous, tendinous, or planar.[3] Eruptive xanthomas are acute, inflammatory lesions that appear rapidly in groups of papules and then disappear over several weeks. Tuberoeruptive and tuberous xanthomas are often grouped together in reports, and they are associated with various hyperlipoproteinemia states. They appear as red, inflamed papules that coalesce. The predilection of these lesions to particular anatomic regions such as the elbows or palms can be pathognomonic for specific types of hyperlipoproteinemia.[3]

These lesions are also reported to resolve spontaneously, although this may only occur after several months. Tendinous xanthomas commonly affect the Achilles tendons, elbows, and extensor tendons of the hand.[5] These are very gradually progressive lesions that bear a strong association with familial hypercholesterolemia. The heterozygous form of this disease is associated with a better prognosis than the homozygous form in which patients have high mortality rates at younger ages. Cerebrotendinous xanthomatosis, as previously described, represents a form of this presentation. This condition can present with neurologic findings such as corticospinal tract signs, cognitive decline, and gait difficulty.[10]

Planar xanthomas can be on the palmar creases and flexure surfaces of fingers, and skin folds and are typically seen with biliary cirrhosis. They can occur in a variety of anatomic regions and can be pathognomonic for different systemic conditions based on their presentation. For example, palmar crease xanthomas can be pathognomonic for familial dysbetalipoproteinemia type III.[3] Xanthoma planum lesions can be spread on large planes of the body. Xanthoma diabeticorum can be seen with severe diabetes and verrucous xanthoma is often seen in association with histiocytes in connective tissues.

Evaluation

On the initial clinical presentation of patients with xanthomas, an evaluation must focus on both locoregional and systemic disease. For the locoregional lesion, a clinical exam is often enough to make a ready diagnosis of xanthoma. Radiographs are typically normal in these patients. Ultrasound study may be performed of tendinous xanthomas, and advanced imaging in the form of magnetic resonance imaging (MRI) may be helpful to rule out differential diagnoses and for surgical planning. Upon diagnosis of xanthoma, a systemic workup must be undertaken simultaneously.

Early recognition of morbid conditions such as familial hypercholesterolemia can avoid delays in management. Therefore, prompt workup by the treating clinician should start with laboratory investigations that include plasma triglycerides, plasma cholesterol, serum LDL, and high-density lipoproteins (HDL). These tests should preferably be performed under fasting conditions and as per other collection and processing standards prescribed by the local laboratory. Specific clinical patterns of presentation such as diffuse plane xanthomas or palmar crease xanthomas should warrant investigation for known pathognomonic conditions that are associated with such findings. As part of the workup for metabolic syndrome, blood glucose and hemoglobin A1c may also be performed as indicated.

Treatment / Management

The main treatment for xanthomas is for the associated medical conditions that produce these lesions. On occasion, surgical excisional biopsy of these lesions may be performed for symptomatic lesions or to exclude other differential diagnoses. It has been reported that identifying the specific lipid type in a lesion can help with the diagnosis of the broader systemic condition underlying this finding. In symptomatic lesions such as tendinous xanthomas over areas that sustain frequent contact with the external environment (for example, shoe wear in Achilles tendon lesions), complete excision in tandem with medical stabilization of the underlying systemic disease process is preferred in order to minimize the risk of recurrence.[8]

In areas such as the Achilles tendon, where wound healing may be difficult after lesion excision, it is imperative to exercise careful soft tissue management and optimize wound closure techniques (including the potential use of flaps).[11] In medical management, the primary objective is to optimize the lipid profile of the patient. HMG-CoA reductase inhibitors have been quite successful in this regard and have the dual benefit of controlling hyperlipidemia while potentially decreasing the size of xanthomatous lesions.[12]

Interestingly, reports of spontaneous resolution of smaller xanthomas have been described following liver transplant and plasmapheresis. These findings again emphasize the importance of controlling the systemic disease as the primary objective. Newer treatment options have emerged in the treatment of these metabolic diseases. For example, monoclonal antibodies against the proprotein convertase subtilisin/kexin type 9 gene have been found to be effective agents in familial hypercholesterolemia.[2] Treatment of xanthoma disseminatum with 2-chlorodeoxyadenosine is another promising agent that has recently been described in various reports as being highly effective.[13]

Differential Diagnosis

Rare cases of xanthomas produced by unusual sterol deposits have been reported in the literature. These include the aforementioned cerebrotendinous xanthomatosis (accumulation of cholestanol) and beta-sitosterolemia.[14] These patients also have a higher incidence of atherosclerotic burden, so careful management of both local and systemic disease is essential.[3]

Prognosis

The overall clinical outcomes in patients with xanthomas depends on a variety of factors. Most importantly, the underlying systemic disease must be appropriately managed. Some of the underlying systemic diseases in these patients may have early and high mortality rates, such as homozygous familial hypocholesterolemia. Others may be managed with lifestyle modifications and systemic therapies that can provide substantial improvements in survival rates. In terms of local disease, most smaller xanthoma lesions may either decrease in size or even completely resolve with effective systemic management. For those local lesions which are symptomatic due to their size or anatomic location, recurrence after excision can be minimized by careful surgical planning. Partial resection or debulking has been associated with a very high recurrence rate in these lesions.

Complications

Adverse events in the management of xanthomas are generally related to systemic therapy. For example, the use of HMG CoA reductase inhibitor therapy has a well-known side effect profile. These side effects range from the more commonly reported statin-associated muscle symptoms (including mild myalgia in up to 10% of users) to rarer but more feared complications such as rhabdomyolysis and necrotizing autoimmune myopathy.[15]

Therefore, systemic therapy for patients presenting with xanthomas should be initiated and managed closely by a provider who is able to recognize and manage any adverse effects of such medications. Surgical complications from the excision of xanthomatous lesions are also well described. As tendinous xanthomas tend to develop in areas that are well known to be at high risk for delayed wound healing, careful surgical planning is essential to avoid wound complications and local recurrence.

Deterrence and Patient Education

Patients may present to a dermatologist or surgeon initially, without knowing that the cause of their lesion is an underlying systemic medical condition. Therefore, patient education is essential upon diagnosis. Adequate counseling

must be provided regarding lifestyle modifications, management options, and the need for regular follow-up. Careful management of the lipid and cholesterol profile can provide effective control against the development of new lesions in the same patient. It is demonstrated in various studies that atheromatous deposits are concurrent with xanthoma formation, which could have significant mortality and morbidity associated with it.[16]

Enhancing Healthcare Team Outcomes

An interprofessional team approach is essential upon the diagnosis of xanthomas to ensure optimal outcomes. This involves a comprehensive workup and prompt referral to the appropriate medical and surgical specialists for further management. It is important for treating surgeons to ensure that patients establish care with a medical specialist who can help optimize their lipid profile in the long-term for best outcomes.

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