Investigation and management of xanthoma

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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The word xanthoma is derived from the Greek *xanthos*, meaning yellow in appearance. The derivation is apt as many xanthoma lesions (plaques, papules and nodules) do have a yellowish appearance, but this is not always so. Xanthomas are accumulations of lipid in and under the skin at various sites on the body, although they may rarely occur in noncutaneous sites such as bone or the central nervous system. Xanthoma is sometimes associated with a blood lipid disorder, although not universally so; its presence, however, justifies the need for further investigation.

Types of xanthoma

The different types of xanthoma are:

- xanthelasma (also called xanthoma palpebrarum) – found on the medial side of the eyelids (Figure 1)
- tendon xanthoma – seen on the ankles, dorsum of the hands, elbows and knees (Figures 2a and b)
- eruptive xanthoma – seen on the buttocks, elbows and pressure areas (Figure 3)
- tuberous xanthoma – seen on the elbows, knees and ankles (Figures 4a and b)
- palmar xanthoma – seen in skin creases of the palms and fingers (Figure 5)
- planar xanthoma – seen on any flat body surface (Figure 6)

Corneal arcus – cholesterol deposits in the corneal stroma – is not conventionally defined as xanthoma but is usefully considered in the same context (Figure 7); it was previously known as arcus senilis. An accumulation of lipid in an atheromatous plaque, however, is not called xanthoma, and will not be discussed further here.

Xanthoma formation

In general, xanthomatous lesions contain cholesterol, phospholipid, triglycerides, connective tissue and blood vessels. The origin of some xanthoma lipids from the bloodstream has been confirmed by various experimental techniques. An underlying mechanism of xanthoma formation appears to be phagocytosis of lipoproteins by macrophages in the interstitial spaces.

How common is xanthoma?

Xanthelasma occurs in around 1% of the general population, and corneal arcus in perhaps 30%. In one US study of men older than 50 years, the average

IN SUMMARY

- **Xanthoma around the eyelids (xanthelasma) is a common presentation in general practice; tendon xanthoma and cutaneous xanthoma are quite rare.**
- **Many patients with xanthoma have an underlying blood lipid disorder.**
- **All patients with xanthoma should have a fasting lipid profile and a standard haematology and biochemistry work up.**
- **Ongoing management is related to any lipid disorder diagnosed.**
- **Specialist referral may be desirable for severe lipid disorders.**

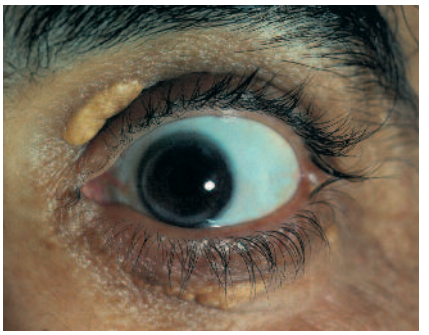
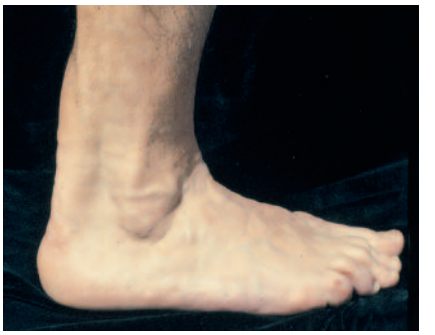
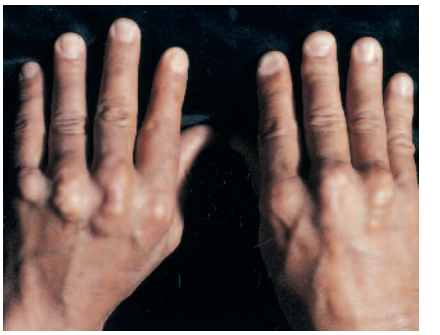


Figure 1. Xanthelasma on the upper eyelid.





Figures 2a and b. Tendon xanthoma on the ankle and hands.

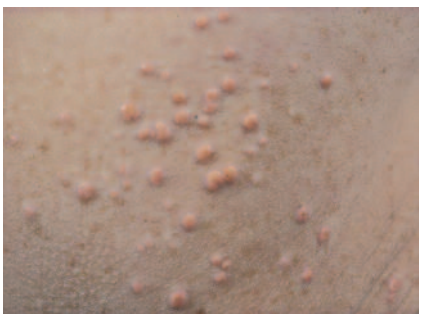
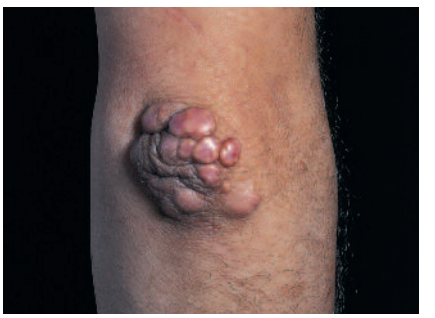
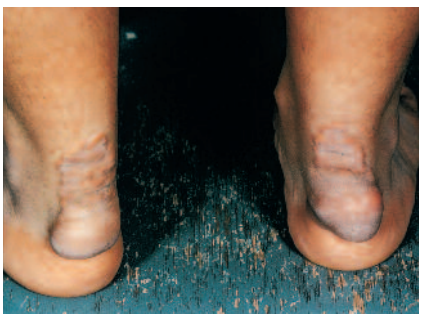


Figure 3. Eruptive xanthoma on buttocks.





Figures 4a and b. Tuberous xanthoma on the elbow and ankles

cholesterol level in those with xanthelasma was 5.9 mmol/L compared with 5.5 mmol/L in those without, suggesting that the broad lipid profile in those with and without xanthelasma is fairly similar. Most of the patients in this study, with or without xanthelasma, were still hypercholesterolaemic, depending on the definition of hypercholesterolaemia. Xanthelasma may become a cosmetic problem for some patients and may not improve with medical treatment alone. Prevalence of corneal arcus increases with advancing age, and when present at a younger age (say below 50 years) is more commonly associated with hypercholesterolaemia.

Other types of xanthoma are significantly less common than xanthelasma and corneal arcus, and are generally only commonly seen in specialised clinics. In these instances, one will be dealing with rarer blood lipid disorders that will be more severe and clinically important.

Xanthoma and lipid disorder associations

Tendon xanthoma

Tendon xanthoma is the hallmark of familial hypercholesterolaemia, an autosomal dominant condition that is highly associated with atheromatous cardiovascular disease. Virtually all patients with familial hypercholesterolaemia seen in clinical practice are of the heterozygous variety. The lesions may occasionally become inflamed and give rise to tendonitis. Tendon xanthoma may or may not regress with specific treatment.

Eruptive xanthoma

Eruptive xanthoma is the hallmark of chronic and severe hypertriglyceridaemia (often exceeding 20 mmol/L). Also known as type V hyperlipoproteinaemia, it is associated with creamy serum (Figure 8), fatty liver, an increased risk of acute pancreatitis and, possibly, an increased risk of cardiovascular disease (a controversial association). The condition usually has a hereditary basis, but with possible exacerbation by diabetes, alcohol sensitivity or obesity. The multiple lesions usually regress rapidly with specific treatment.

Tuberous xanthoma

Tuberous xanthoma is occasionally seen in familial hypercholesterolaemia and more rarely

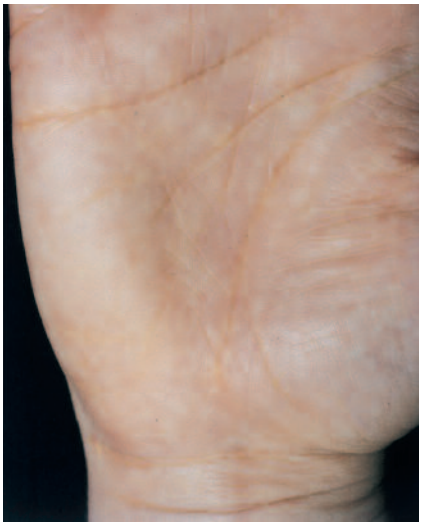


Figure 5. Palmar xanthoma.

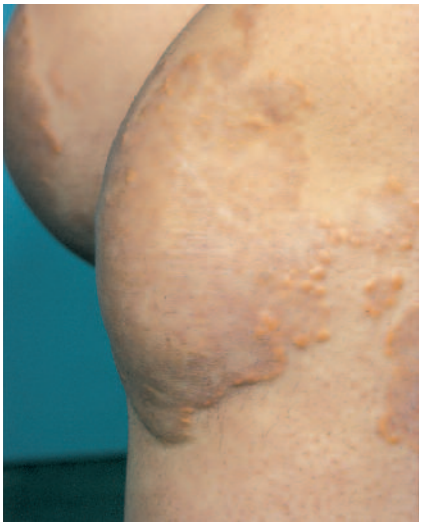


Figure 6. Planar xanthoma on the knees.

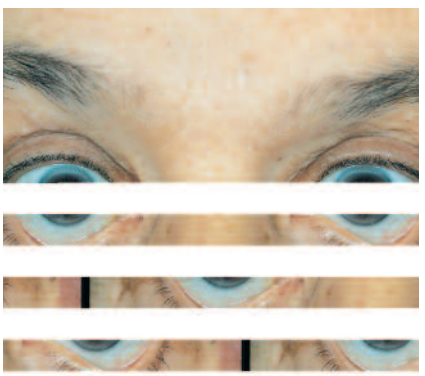


Figure 7. Corneal arcus.

Figure 8. Creamy, lipaemic serum in severe hypertriglyceridaemia.

in severe hypertriglyceridaemia. It may regress with specific treatment.

Palmar xanthoma

Palmar xanthoma is the hallmark of primary dysbetalipoproteinaemia (previously known as broad beta disease or type III hyperlipoproteinaemia). These patients are homozygous for the *apo-E2* allele. The lesions rapidly regress with specific treatment.

Planar xanthoma

Planar xanthoma is occasionally seen in familial hypercholesterolaemia, particularly the very rare homozygous variety.

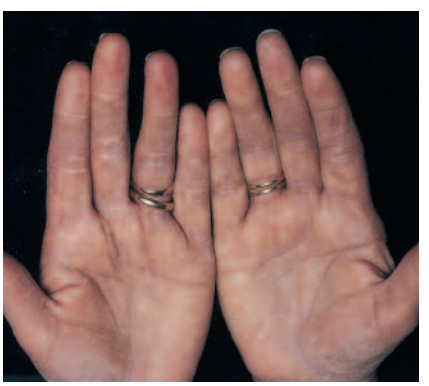


Figure 9. Palmar xanthoma in primary biliary cirrhosis.

Other associations

A florid form of palmar xanthoma occurs in primary biliary cirrhosis (Figure 9), but this condition can be easily differentiated from primary dysbetalipoproteinaemia on other grounds.

Tendon xanthoma may also occur in two other extremely rare conditions, cerebrotendinous xanthomatosis and familial sitosterolaemia. A clue to these syndromes might be tendon xanthoma in the presence of a normal cholesterol level. More information may be found in a standard textbook of medicine.

Investigations

All xanthomas should be investigated because the patient may have significant underlying metabolic disease. The following initial investigations should be performed in a patient with suspected xanthoma:

- clinical and family history
- fasting lipid profile – cholesterol, triglycerides, HDL and LDL cholesterol
- standard haematology and biochemistry work up (with special reference to glucose and liver function tests).

Apo-E genotyping may be required later in some patients.

The finding of a lipid disorder will explain the presence of xanthelasma, and likewise the finding of familial hypercholesterolaemia, the presence of tendon lesions. In patients with familial hypercholesterolaemia, there will be elevated total and LDL cholesterol levels, and average or minimally raised triglycerides levels. In patients with eruptive xanthoma, there will be triglycerides levels above 10 to 20 mmol/L, and highly variable cholesterol levels. Follow up blood tests may be required to exclude other conditions, such as hypothyroidism.

Although appropriate blood testing will eliminate the need for biopsy in most cases, sometimes a xanthoma may be diagnosed only after lesion biopsy.

Management

Xanthelasma may be of cosmetic concern to some patients, and lesions may enlarge over time. Surgical excision should usually be accompanied by lipid modifying therapy as otherwise recurrence may be a problem.

Other xanthomas are usually manifestations of underlying metabolic problems and these should receive specific management. While it is beyond the scope of this article to cover details of lipid management, the following points are appropriate in relation to xanthoma:

- familial hypercholesterolaemia will need dietary advice and usually drug therapy with a statin
- marked hypertriglyceridaemia and also primary dysbetalipoproteinaemia will need dietary advice and usually drug therapy with a fibrate
- specialist referral may be required for more severe lipid disorders
- all therapy must be permanent and long term compliance supported.

Conclusion

Xanthoma around the eyelids is a common presentation that is seen in clinical practice, while tendon and cutaneous xanthomas are quite rare. Xanthoma is often associated with a blood lipid disorder and further investigation is necessary. Ongoing management will be related to any lipid disorder diagnosed. Specialist referral may be required for severe lipid disorders. MT

DECLARATION OF INTEREST: None.

Table. Xanthomas and associated lipid disorders

Xanthelasma	May be associated with hypercholesterolaemia
Corneal arcus*	May be associated with hypercholesterolaemia, especially in patients under 50 years of age
Tendon xanthoma	Associated with familial hypercholesterolaemia
Eruptive xanthoma	Associated with chronic and severe hypertriglyceridaemia
Tuberous xanthoma	Occasionally associated with familial hypercholesterolaemia and rarely with severe hypertriglyceridaemia
Palmar xanthoma	Associated with primary dysbetalipoproteinaemia and primary biliary cirrhosis
Planar xanthoma	Occasionally associated with familial hypercholesterolaemia

* Corneal arcus is not conventionally defined as xanthoma but is usefully considered in the same context.