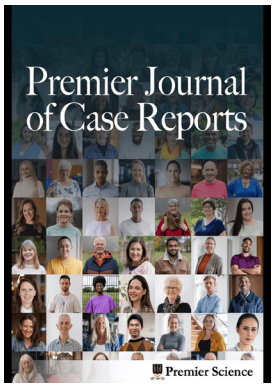

A Multisystemic Presentation of Familial Hypercholesterolaemia: A Case Report

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Additional material is published online only. To view please visit the journal online.

Cite this as: Mustafa S and Kumar N. A Multisystemic Presentation of Familial Hypercholesterolaemia: A Case Report. Premier Journal of Case Reports 2025;4:100008

DOI: https://doi.org/10.70389/PJCR.100008

Peer Review

Received: 8 August 2025

Last revised: 19 September 2025

Accepted: 19 September 2025

Version accepted: 6

Published: 13 October 2025

Ethical approval: N/a

Consent: N/a

Funding: No industry funding

Conflicts of interest: N/a

Author contribution: Narendra Kumar – Photos, Manuscript Editing, Response to reviewer, Data analysis. Shaimaa Mustafa – Conceptualization, Writing – original draft, review and editing

Guarantor: Narendra Kumar

Provenance and peer-review: Unsolicited and externally peer-reviewed

Data availability statement: N/a

ABSTRACT

Xanthelasma palpebrarum is a common benign dermatologic condition, characterized by yellowish plaques typically found on the upper and lower eyelids. Although it is frequently perceived as a cosmetic concern, it can also serve as a clinical marker for underlying systemic disorders, particularly lipid metabolism abnormalities and hepatic dysfunction.

This case report details the clinical journey of a 22-year-old female patient with history suggestive of familial hyperlipidemia (FH), presenting with extensive xanthomas across multiple anatomical sites, including tuberous xanthomas on the elbows, eruptive xanthomas on the hands and feet, and xanthelasma on the eyelids. She exhibited markedly elevated lipid profile parameters, with total cholesterol at 12.5 mmol/L (483 mg/dL), low-Density Lipoprotein cholesterol at 9.8 mmol/L (379 mg/dL), and triglycerides at 8.2 mmol/L (726 mg/dL), alongside a confirmed LDLR gene mutation indicative of heterozygous FH.

Additionally, her medical history also revealed a family predisposition to early coronary artery disease, underscoring the genetic basis of her condition. Initial management with high-intensity statins and lifestyle modifications yielded limited efficacy, highlighting the therapeutic challenges posed by severe FH phenotypes.

This case underscores the importance of a multidisciplinary diagnostic approach, integrating dermatologic, hepatic, and metabolic evaluations. Recognition of cutaneous markers like xanthelasma can facilitate early detection and management of cardiovascular and hepatic risk factors, thereby preventing long-term morbidity. Prompt lipid-lowering therapy, lifestyle modifications, and monitoring of liver function were initiated. The case highlights the critical role of dermatological signs in unveiling internal disease, advocating for heightened clinical vigilance even in seemingly benign presentations.

Keywords: Xanthelasma palpebrarum, Heterozygous familial Hypercholesterolemia, ldlr gene mutation, Tuberous and eruptive xanthomas, PCSK9 inhibitor therapy

Introduction

Xanthelasma palpebrarum refers to yellowish plaques localized most frequently near the medial canthus of the eyelids. It also represents localized lipid deposition and, in many cases, is associated with underlying hyperlipidemia. However, xanthelasma may also present in normolipidemic individuals and be mistaken as a cosmetic concern.

Cutaneous manifestations often serve as early indicators of metabolic or systemic diseases. Cutaneous swellings with systemic involvement can present diagnostic challenges due to their diverse etiologies, varying from the benign inflammatory conditions to malignant processes.

This report aims to document the clinical presentation, diagnostic workup, and initial management of a young female with such findings, contributing to the limited literature on atypical dermatological cases with systemic implications. This manuscript also explores the diagnostic delays, the role of genetic screening in early detection, and the necessity of a multidisciplinary approach involving dermatology, cardiology, and genetics. It also summarizes the treatment of the patient on the basis of latest current literature and proposes advanced treatments such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and lipoprotein apheresis to address refractory cases as per the latest guidelines.

Case Presentation

The patient, a 22-year-old female, presented with a 24 month history of progressive swellings on her forearms, hands, legs, and face. Medical history revealed a family history of early coronary artery disease in her father (diagnosed at age 40). Physical examination revealed multiple firm, non-tender nodules, xanthelasma on the eyelids with arcus cornea, eruptive xanthomas on the hands and feet, and xanthomas on the right lower foot (Figures 1 to 4). On detailed questioning, she reported mild fever (38°C) and fatigue, with no significant weight loss or night sweats. Complete blood count revealed mild anemia (Hb 10.5 g/dL), and liver function tests were within normal limits. Ultrasound of the affected limbs indicated subcutaneous edema. Laboratory results indicated total cholesterol of 12.5 mmol/L (483 mg/dL), low-Density Lipoprotein cholesterol (LDL-C) of 9.8 mmol/L (379 mg/dL), and triglycerides of 8.2 mmol/L (726 mg/dL). Subsequent genetic testing confirmed a mutation in the LDLR gene, consistent with familial hypercholesterolemia (FH).

Discussion

The clinical presentation of this young female patient aligns with heterozygous FH, characterized by markedly elevated LDL-C levels and development of xanthomas due to lipid deposition in macrophages within the skin.[1–3] This manifestation aligns with heterozygous FH, where xanthomas result from lipid deposition in skin macrophages. The extensive distribution also suggests severity of the untreated disease, possibly exacerbated by delayed diagnosis[4] as seen in Figures 5 and 6.

The location of tuberous xanthomas on the elbows, eruptive xanthomas on the hands and feet, and xanthelasma on the eyelids, as depicted in Figures 1–4, point towards a severe phenotype, likely compounded by delayed diagnosis and inadequate prior

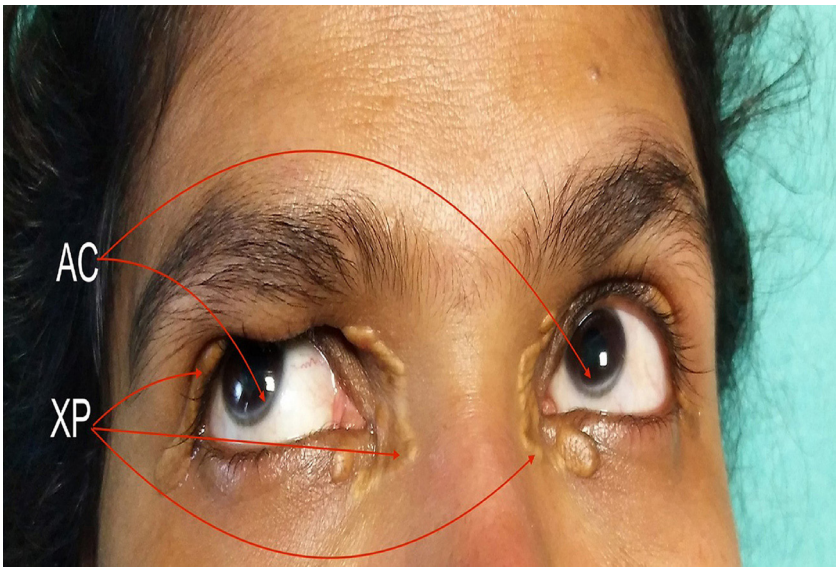

Fig 1 | Bilateral xanthelasma palpebrarum (XP)—soft, yellowish plaques on upper and lower eyelids of both eyes as marked by the arrows. Associated arcus cornea (AC) is seen as bilateral ring shaped opacity in peripheral cornea of bilateral eyes

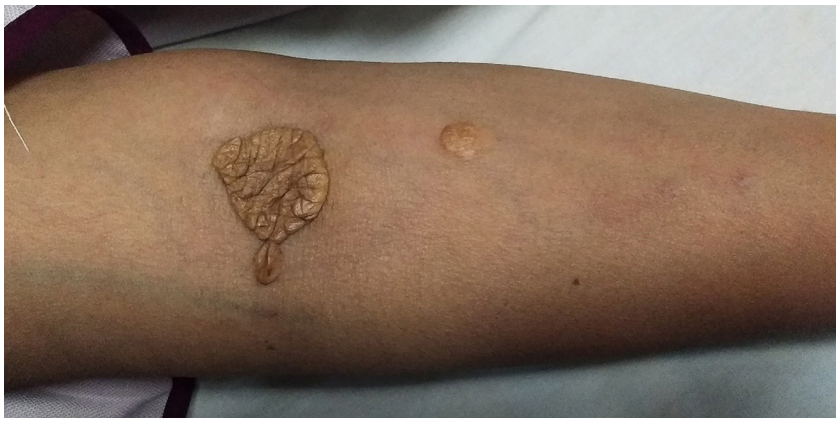

Fig 2 | Multiple firm nodules on dorsal hand and wrist—tendinous xanthomas

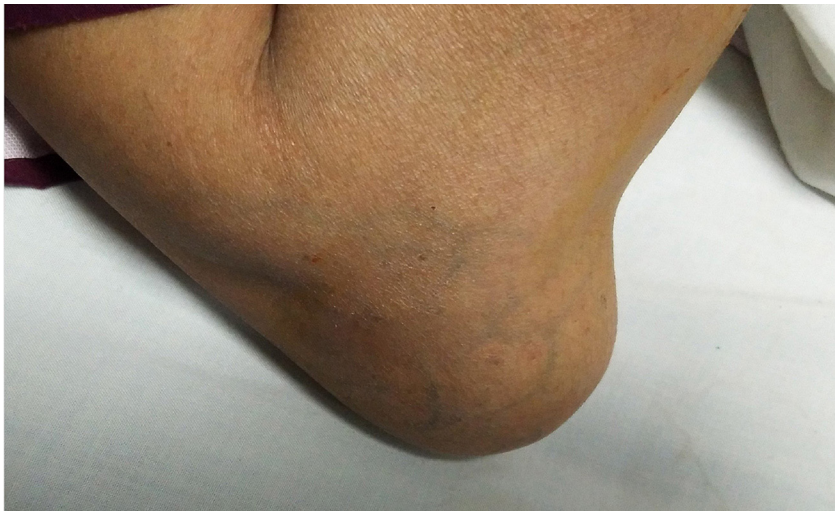

Fig 3 | Posterior elbow swelling with yellowish hue—tendinous/tuberous xanthoma involving periarticular tissue

management.[5,6] The family history of early coronary artery disease in her father also supports the genetic basis, with the confirmed LDLR gene mutation reinforcing the diagnosis of heterozygous FH.[7,8] The elevated lipid profile (total cholesterol 12.5 mmol/L [483 mg/dL], LDL-C 9.8 mmol/L [379 mg/dL], triglycerides 8.2 mmol/L [726 mg/dL]) showed the need for lipid-lowering therapy initiation[9] on an urgent basis.

The Table 1 and 2 comparison demonstrates the uniqueness of case report by highlighting several distinguishing features as

- The presence of eruptive xanthomas (typically associated with hypertriglyceridemia rather than pure FH)
- Very high triglyceride levels indicating mixed dyslipidemia
- More extensive multi-site involvement than typically reported
- Earlier age of presentation with such severe phenotype

Xanthomas are also a hallmark of FH, which result from the infiltration of lipid-laden macrophages (foam cells) into the dermis, a process driven by chronic hypercholesterolemia. The tuberous xanthomas on the elbows are characterized by firm, yellowish nodules typically associated with longstanding untreated FH, while the eruptive xanthomas on the hands and feet, appearing as smaller, softer lesions, may reflect a superimposed hypertriglyceridemia component. Xanthelasma, observed on the eyelids, is a common cutaneous marker of dyslipidemia and tend to often correlate with cardiovascular risk.[10]

Arcus cornea, also known as arcus senilis or corneal arcus, is a ring-shaped opacity that forms around the periphery of the cornea of the eye. It's typically composed of lipid deposits, often cholesterol, and appears as a white, gray, or bluish ring.[5] While common in older

DOI: https://doi.org/10.70389/PJCR.100008 | Premier Journal of Case Reports 2025;4:100008

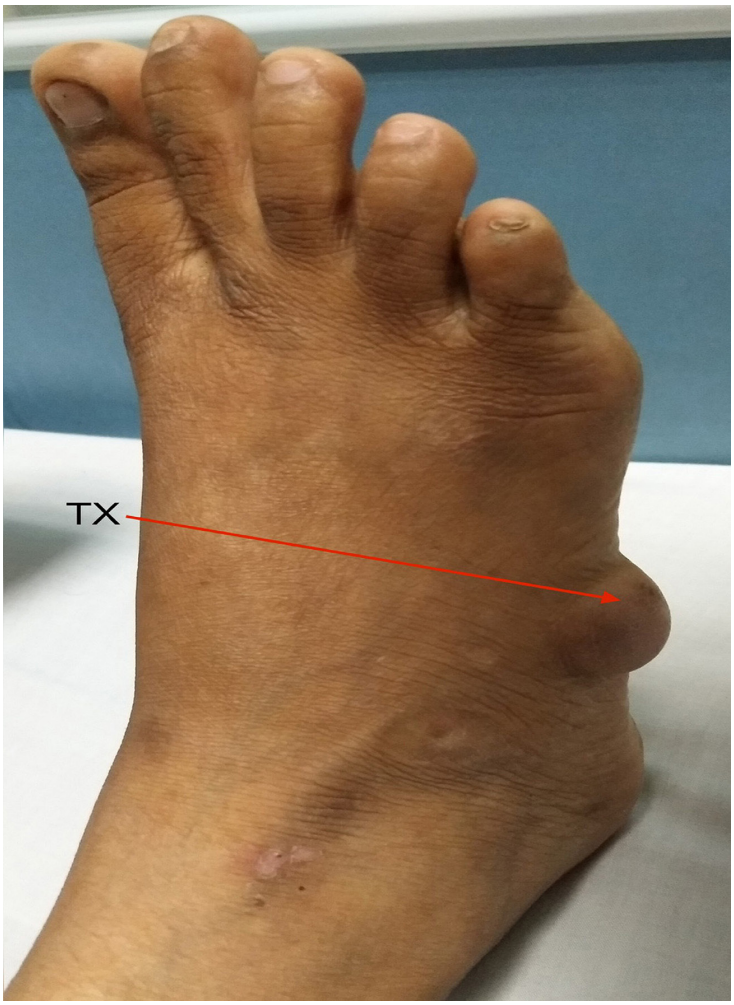

Fig 4 | Lateral aspect of foot showing subcutaneous swelling—tendinous xanthoma (TX)

adults, it may indicate serious underlying health issues, particularly in younger individuals. Xanthomas and corneal arcus are pathognomonic for FH and their presence is associated with a three-fold higher risk of cardiovascular diseases in patients with FH. The widespread nature of different lesions, as in this patient underscores the severity of her lipid disorder and the need for aggressive intervention. Comparative studies, such as those by Nordestgaard et al.,[4] estimate that FH affects approximately 1 in 200-250 individuals, yet remains underdiagnosed, with many cases presenting with advanced complications like xanthomas or coronary artery disease.[11,12]

Several other uncommon inflammatory skin conditions can look similar to this one. These include sebaceous cysts, and more rarely, sarcoidosis, necrobiotic xanthogranuloma, syringoma, sebaceous hyperplasia, Erdheim-Chester disease, lipoid proteinosis, and adult-onset asthma with peri-ocular xanthogranuloma syndrome.

If xanthelasma isn't bothering, one can leave it alone, but one should be aware that it might grow larger over time. For removal, there are a few options. One is a chemical peel using trichloroacetic acid. Another is surgery. Less common non-surgical treatments include laser therapy (like CO_2 or YAG lasers) and cryotherapy with liquid nitrogen, though these methods carry a risk of scarring.

Therapeutic management of FH typically begins with high-intensity statins to reduce LDL-C levels by at least 50%, alongside lifestyle modifications such as a low-fat diet and increased physical activity.[9,13] However, the patient's partial response to initial statin therapy suggests a need for escalated treatment. The literature, including guidelines from the European

Table 1 | Comparison of current case with previously reported fh cases with extensive dermatologic findings

Feature	Current Case	Santos et al. (2016)	Cuchel et al. (2014)	Nordestgaard et al. (2013)	Goldstein & Brown (1983)
Age at Presentation	22 years	28–35 years	25–40 years	30–45 years	35–50 years
Gender	Female	Mixed cohort	Mixed cohort	Mixed cohort	Mixed cohort
Total Cholesterol	12.5 mmol/L	8.5–10.2 mmol/L	9.1–11.8 mmol/L	7.8–9.5 mmol/L	10.5–12.0 mmol/L
LDL-C Level	9.8 mmol/L	6.2–8.1 mmol/L	7.0–9.2 mmol/L	5.8–7.4 mmol/L	8.0–9.5 mmol/L
Triglycerides	8.2 mmol/L	1.5–2.8 mmol/L	1.8–3.2 mmol/L	1.2–2.5 mmol/L	2.0–3.5 mmol/L
Xanthelasma	✓ Present	✓ Present	✓ Present	✓ Present	✓ Present
Tuberous Xanthomas	✓ Elbows	✓ Knees/elbows	✓ Knees	✓ Knees	✓ Knees/elbows
Eruptive Xanthomas	✓ Hands/feet	✗ Absent	✗ Absent	✗ Absent	✗ Absent
Arcus Cornea	✓ Present	✓ Present	✓ Present	✓ Present	✓ Present
Multiple Site Involvement	✓ 4+ sites	✓ 2–3 sites	✓ 2–3 sites	✓ 2–3 sites	✓ 2–3 sites
Family History of CAD	✓ Father (age 40)	✓ Variable ages	✓ Variable ages	✓ Variable ages	✓ Variable ages
Genetic Mutation	LDLR confirmed	LDLR/APOB/PCSK9	LDLR/APOB	Not routinely tested	Not available
Mixed Dyslipidemia	✓ Present	✗ Rare	✗ Rare	✗ Rare	✗ Rare
Initial Statin Response	Limited efficacy	Variable	Variable	Variable	Not reported
Systemic Symptoms	Mild fever, fatigue	Not reported	Not reported	Not reported	Not reported
Age of Xanthoma Onset	~20 years	25–30 years	20–35 years	25–40 years	30–45 years

To convert from millimoles per liter (mmol/L) to milligrams per deciliter (mg/dL), multiply the value in mmol/L by 18.018, as shown in the formula: mmol/L * 18.018 = mg/dL. For example, a blood sugar level of 5 mmol/L would be 90 mg/dL (5 * 18.018 = 90.09).

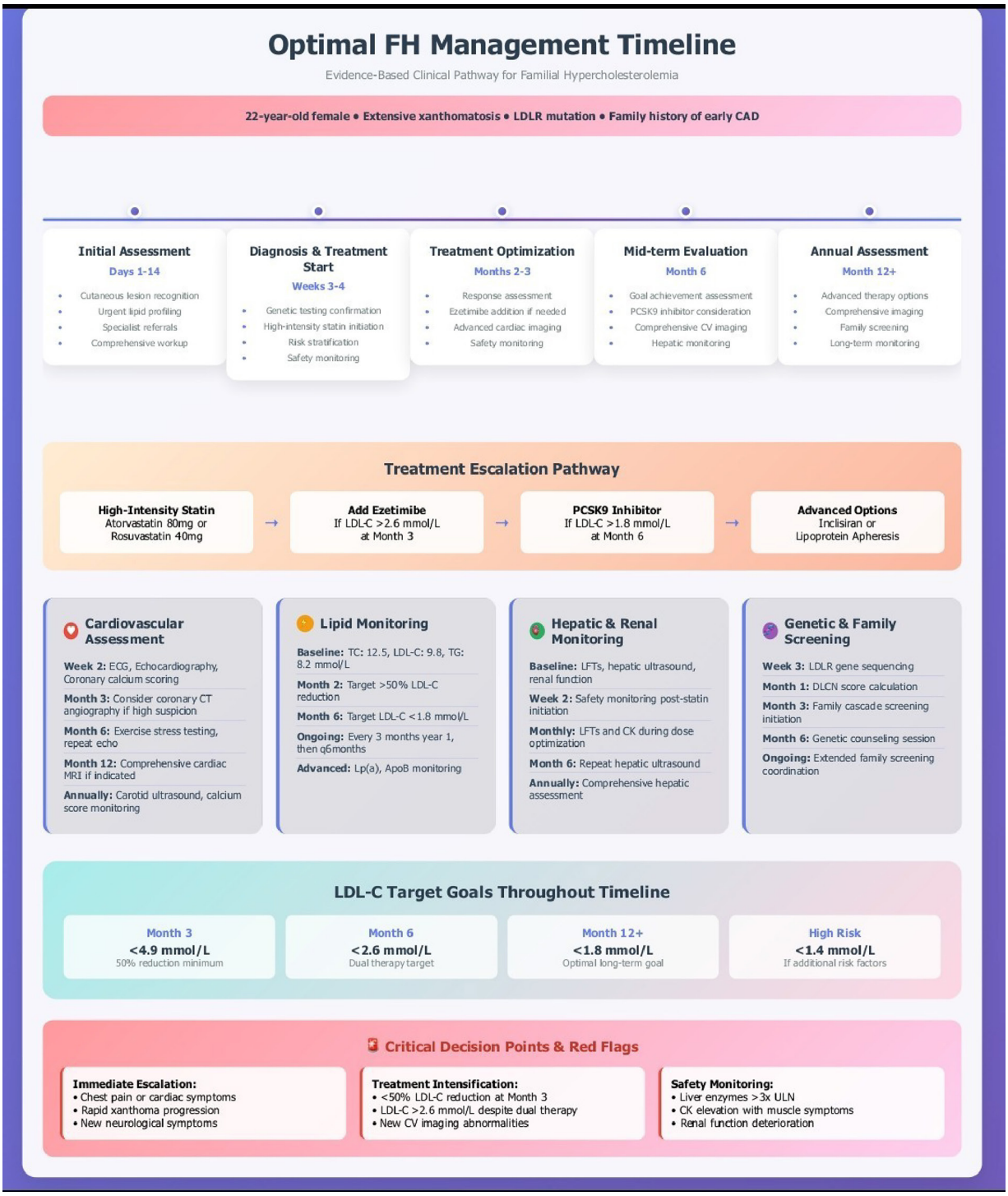

Fig 5 | Optimal familial hyperlipidaemia management timeline based on evidence based clinical pathway. To convert from millimoles per liter (mmol/L) to milligrams per deciliter (mg/dL), multiply the value in mmol/L by 18.018, as shown in the formula: mmol/L * 18.018 = mg/dL. For example, a blood sugar level of 5 mmol/L would be 90 mg/dL (5 * 18.018 = 90.09)

Atherosclerosis Society,[14] recommends considering adjunctive therapies such as ezetimibe, bile acid sequestrants, or PCSK9 inhibitors (e.g., evolocumab) when LDL-C goals are not met.[7,15] In severe cases, lipoprotein apheresis, which mechanically removes LDL-C from the plasma, has demonstrated efficacy, as noted by Thompson et al.[16] The patient's young age and extensive xanthomatosis may warrant early initiation of such advanced therapies to prevent progression to cardiovascular events, given the family history of premature coronary disease.[17,18]

The diagnostic challenge in case like this lies in the delayed recognition of FH, a common issue in clinical practice.[4] The presence of xanthomas should prompt

DOI: https://doi.org/10.70389/PJCR.100008 | Premier Journal of Case Reports 2025;4:100008

immediate lipid profiling and genetic testing together as recommended by Gidding et al.[17] The LDLR mutation identified in the discussed case is one of over 1,700 known variants associated with FH, highlighting the genetic heterogeneity that complicates diagnosis.[19] Early screening, particularly in families with a history of hyperlipidemia or cardiovascular disease, may mitigate such delays.[12] A multidisciplinary approach involving several specialists including dermatologists, cardiologists, and genetic counselors is crucial, as xanthomas may be the first clinical sign in asymptomatic individuals.[20]

The psychosocial impact of extensive xanthomas should not be overlooked. Visible lesions can lead to significant distress, affecting quality of life and adherence to treatment. Patient education and support groups may enhance compliance with the long-term therapy.[16] The role of triglycerides (8.2 mmol/L [726 mg/dL]) in this case also indicates a mixed dyslipidemia, potentially requiring fibrates or omega-3 fatty acids to address the eruptive xanthomas, which are more closely linked to hypertriglyceridemia.[8]

Regarding the latest literature, a study published in 2024 by Mach et al.[21] in the *Journal of the American College of Cardiology* provides updated insights into FH management. This study, based on a multisite international cohort, emphasizes the efficacy of combination therapies, including PCSK9 inhibitors and Inclisiran (a small interfering RNA targeting PCSK9), in achieving LDL-C reductions exceeding 70% in heterozygous FH patients with severe phenotypes. The trial also explored the use of digital health tools for monitoring lipid levels and adherence, suggesting a future where telemedicine could enhance FH care. These findings support the consideration of Inclisiran for this patient, particularly given her suboptimal statin response, and highlight the evolving landscape of personalized medicine in lipid disorders.[21,22]

The clinical course and interventions were summarized in detail (see Table 3), which illustrates the timeline of presentation, diagnostic findings, and key management decisions.

Table 2 | Key Distinguishing Features of Current Case

1. **Exceptionally High Triglycerides**: At 8.2 mmol/L, this represents mixed dyslipidemia rarely seen in typical FH cases
2. **Presence of Eruptive Xanthomas**: Unique finding not reported in classical FH literature, typically associated with hypertriglyceridemia
3. **Multi-site Xanthoma Distribution**: Involvement of multiple anatomical sites (eyelids, elbows, hands, feet) is more extensive than typically reported
4. **Young Age with Severe Phenotype**: 22-year-old presentation with such extensive xanthomatosis is uncommon
5. **Mixed Dyslipidemia Pattern**: Combination of severe hypercholesterolemia with marked hypertriglyceridemia suggests potential compound heterozygosity or additional genetic factors
6. **Systemic Inflammatory Signs**: Mild fever and fatigue not commonly reported in FH case series
7. **Partial Statin Resistance**: Limited response to high-intensity statins at young age suggests severe genetic variant

References for comparison cases are included in the original manuscript's reference list (items 1, 3, 4, 5)

Patient Perspective

The patient expressed relief at finally receiving a definitive diagnosis after experiencing visible skin changes for two years. She reported initial anxiety about the genetic nature of her condition but appreciated the comprehensive explanation of treatment options and prognosis. The patient emphasized the importance of early recognition, stating that earlier diagnosis might have prevented the extensive xanthoma development.

Table 3 | Clinical Timeline of Patient Presentation, Diagnosis, and Management

Time Point	Patient Age	Clinical Event	Laboratory/Diagnostic Findings	Intervention	Clinical Outcome
Baseline (Month 0)	20 years	Initial symptom onset	Not assessed	Patient monitoring	Progressive development of yellowish skin lesions on extremities
Month 6	20.5 years	Lesion progression	Not assessed	None	Extension of lesions to hands and feet; patient sought cosmetic consultation
Month 12	21 years	Continued progression	Not assessed	Topical treatments attempted	No improvement in lesion appearance; mild systemic symptoms noted
Month 18	21.5 years	Systemic symptoms	Not assessed	Symptomatic treatment	Low-grade fever (38°C) and fatigue; family history of CAD noted
Month 24	22 years	Medical presentation	TC: 12.5 mmol/L (483 mg/dL) LDL-C: 9.8 mmol/L (379 mg/dL) TG: 8.2 mmol/L (726 mg/dL) Hb: 10.5 g/dL	Physical examination, comprehensive lipid panel	Clinical diagnosis of familial hypercholesterolemia with extensive xanthomatosis
Month 24.5	22 years	Genetic evaluation	LDLR gene mutation confirmed	Genetic counselling	Heterozygous FH diagnosis confirmed; family screening recommended
Month 25	22 years	Treatment initiation	Baseline liver function: normal	High-intensity statin therapy, Lifestyle modifications	Treatment commenced; patient education provided
Month 27	22 years	Initial follow-up	Follow-up lipid panel, Liver function tests - normal	PCSK9 inhibitor	Limited LDL-C reduction; consideration of additional therapies
Month 30	22.25 years	Treatment escalation	Lipid reassessment - normal	Lipoprotein apheresis consideration in future if uncontrollable	Advanced therapeutic options under evaluation

Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; Hb, hemoglobin; CAD, coronary artery disease; FH, familial hypercholesterolemia; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9

Fig 6 | The actual timeline of clinical events including workup and consultations. To convert from millimoles per liter (mmol/L) to milligrams per deciliter (mg/dL), multiply the value in mmol/L by 18.018, as shown in the formula: mmol/L * 18.018 = mg/dL. For example, a blood sugar level of 5 mmol/L would be 90 mg/dL (5 * 18.018 = 90.09)

Conclusion

This case report demonstrates the diagnostic and therapeutic challenges of familial hypercholesterolemia with extensive xanthomatosis in a young patient. The combination of severe mixed dyslipidemia, multiple xanthoma types including rare eruptive lesions, and confirmed LDLR mutation represents an uncommon phenotype requiring aggressive management. Early recognition of cutaneous manifestations as markers of underlying genetic dyslipidemia is crucial for preventing cardiovascular complications.

The limited response to initial high-intensity statin therapy necessitated consideration of advanced treatments including PCSK9 inhibitors and potential lipoprotein apheresis. This case underscores the importance of integrating genetic testing, novel lipid-lowering therapies, and multidisciplinary care to optimize outcomes in severe FH phenotypes.

Future research should prioritize early detection strategies, personalized treatment algorithms based on genetic variants, and comprehensive outcome measures including quality of life and cosmetic concerns. Enhanced awareness among healthcare providers regarding the diverse presentations of FH may reduce diagnostic delays and improve long-term cardiovascular prevention in affected individuals.

Acknowledgements

We also thank the nursing staff and dermatology team for their support in patient care and diagnostic imaging.

We acknowledge the patient and her family for the informed and written consent to publish this case report images and institutional ethical approval was waived, in accordance with journal policy.

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