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International Journal of Clinical Case Reports and Reviews

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Case Report

Huge and Multiple Xanthomas Misdiagnosed as Rheumatoid Nodules and Mistreated with Multiple Surgical Excisions over 4 Years, A Case Report

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Received Date: August 29, 2024 | **Accepted Date:** September 09, 2024 | **Published Date:** October 14, 2024

Citation: Reham AlGhazo, Khaldown M Alaweneh, Noran K Kofahi, Ali M Ibnian, Ahmad Awad, et al, (2024), Huge and multiple xanthomas misdiagnosed as rheumatoid nodules and mistreated with multiple surgical excisions over 4 years, a case report, *International Journal of Clinical Case Reports and Reviews*, 19(2); **DOI:10.31579/2690-4861/534**

Abstract:

Background: Xanthoma is the iceberg of familial hypercholesterolemia; it's resemblance to other cutaneous lesions such as rheumatoid nodules might lead to misdiagnosis. We emphasize in this case report the importance of comprehensive clinical and investigatory approach to cutaneous lesions as they could be the only manifestation of systemic diseases, and this helps to avoid delayed management and unnecessary interventions.

Aim: Xanthomas as a possible diagnosis for multiple skin nodules, as it can be easily supported by performing simple noninvasive blood tests; the lipid panel.

Case report: Female patient, presented with multiple skin lesions and a strong family history of premature coronary artery disease. She was firstly managed with multiple surgical resections as having benign masses, and later was misdiagnosed as having rheumatoid nodules and referred to rheumatology clinic for evaluation, wherein a clinical suspicion of xanthomas originated, and was supported by the severely elevated serum LDL level and a tissue diagnosis of xanthoma. She has been started on statins with regular clinic.

Conclusion: The purpose of this case study is to explain the importance of including xanthomas within the differential diagnosis of recurrent skin lesions. Whereas the tissue diagnosis is the gold-slandered investigation, simple noninvasive blood test, serum lipid measurement can be the clue for diagnosis of the hidden fatal but easily controllable disease; familial hypercholesterolemia.

Key words: xanthoma; multiple skin nodules; familial hyperlipidemia; unnecessary surgery; misdiagnosis

1. Introduction

Xanthomas are painless slow-growing masses containing lipid-laden macrophages called foam cells [1, 2]. Xanthomas commonly develop at the skin and tendons specifically the extensor surfaces of the elbows, wrists, knees, and ankles; regions exposed to regular mechanical stress [3, 4]. In addition, xanthoma may also appear on other deep connective tissues (e.g., tendon sheath, synovium, and bone), as well as other sites including the stomach, aryepiglottic folds, larynx, and urinary bladder [5-7].

Tendon xanthomas are directly linked to underlying familial hypercholesterolemia (FH) [8]. FH has a large spectrum of genetic mutations and different doses of mutation involvement which impacts the LDL cholesterol level in the blood and the resultant ischemic heart disease (IHD) probability and severity [9-11]; heterozygous FH is more common

and has a prevalence of 1 in 200 - 240 individuals [12-14], whereas homozygous FH is very rare and occurs in approximately 1 in 1 million persons, it is associated with more severe myocardial infarctions. It could occur as early as four years of age [15-17].

Xanthomas are sometimes difficult to distinguish from some cutaneous manifestations of certain rheumatological and dermatological diseases [18, 19], this leads to delayed treatment and more patient frustration. Among the known cutaneous manifestations of medical illnesses, rheumatoid nodules can significantly mimic xanthomas [20, 21].

FH continues to be "hidden in plain sight" with a significant number of children and adults remaining undiagnosed and some are misdiagnosed [22]. Here we report an interesting case of a patient who was diagnosed with FH after four years of being initially labeled as having rheumatoid arthritis nodules, for which she has had multiple unnecessary surgical resection procedures.

2. Case Report:

A 17-year-old female patient was referred to our Rheumatology clinic by her GP for the evaluation of multiple soft and yellow nodular lesions of different sizes, they are painless and distributed over her elbows, knees, ankles, and feet. She reported having these lesions for four years now. They have gradually increased in size, with recurrence after multiple surgical resections.

The presence of these lesions along with some mild and non-specific joint pains misled her primary physician at that time to presume a diagnosis of rheumatoid arthritis with associated rheumatoid nodules. Furthermore, she was also evaluated by a surgeon as having some benign masses managed with multiple surgical resections where no tissue diagnosis attempts were made. The procedures involved the lesions over her elbows and left Achilles's tendon with recurrence requiring a total of 4 resections over the past 4 years. Unfortunately, no clear details could be obtained regarding her previous treatments and investigations apart from this as her family denied being counseled or taught about their daughter's exact problem.

Upon primary evaluation at our clinic, the patient reported mild non-specific arthralgia but no joint swelling or morning stiffness. She has never complained of chest pain, or shortness of breath and has no other previous or current medical illnesses including diabetes, hypertension, or any thyroid disorder. The patient is a daughter of consanguineous healthy parents; she has four healthy siblings with no similar conditions among her family members. However, family history was significant for early sudden deaths and premature coronary artery disease; one of her paternal uncles passed away suddenly at the age of 39, and an elder one has a history of coronary artery disease and had a myocardial infarction when he was 33.

Physical examination showed a patient with well body build and normal vital signs. It revealed multiple non-tenders, yellow-colored masses of varying sizes ranging from 1 to 6 cm, located mainly at the extensor surfaces of her elbows, left wrists, both knees, feet, and Achilles's tendons bilaterally (Figure 1).

The lesions were firm, locally mobile, and not tethered to the overlying skin; their proximity to the joints caused minimal limitation of movement. Arcus lipoides juveniles have also been noticed (Figure 2).

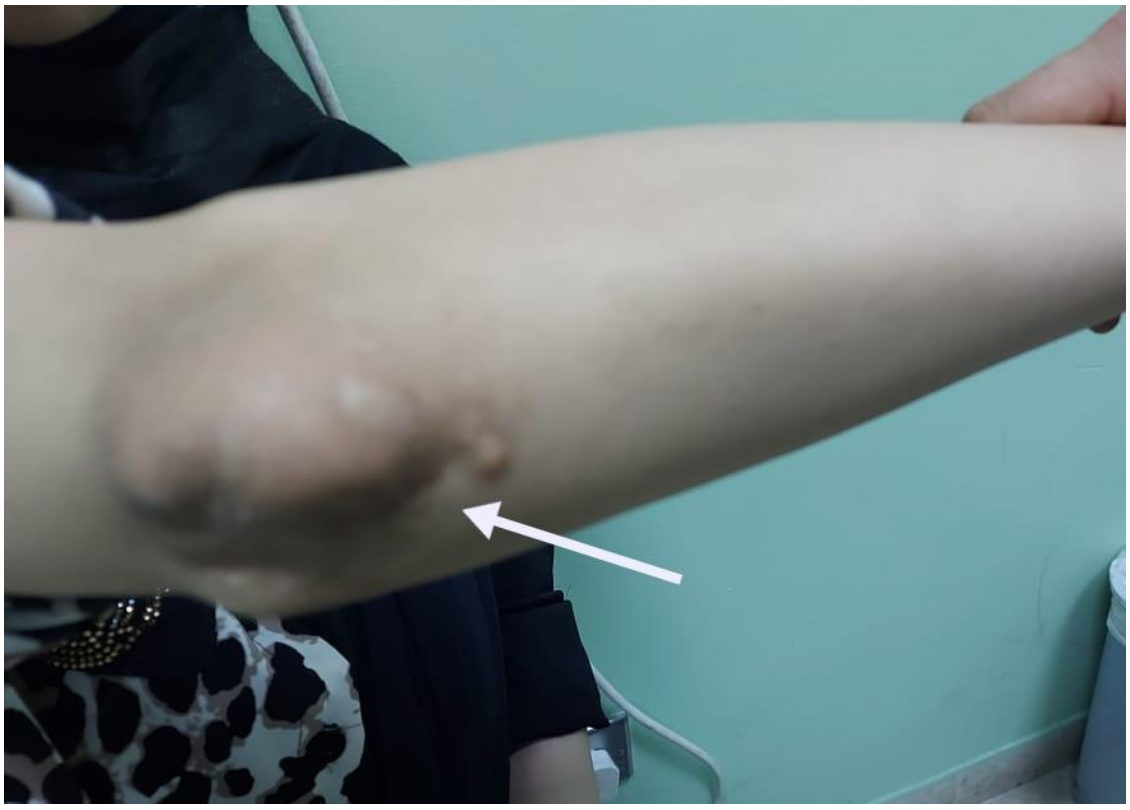

Figure 1 (A): Right elbow

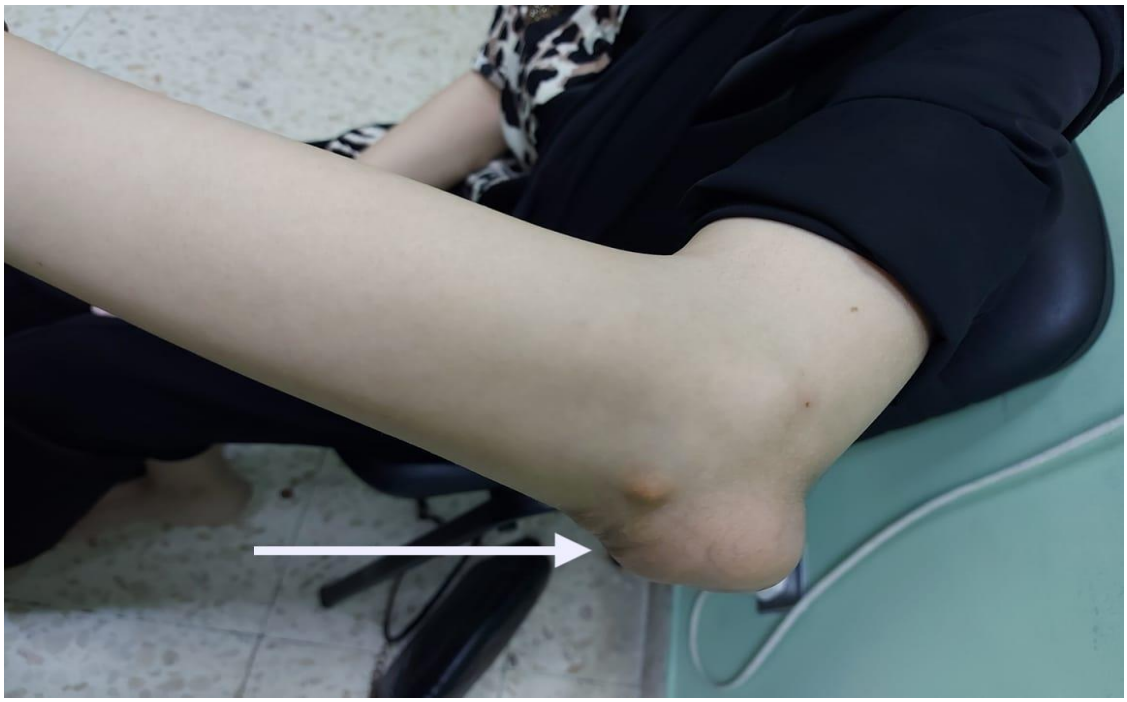

Figure 1(B): Left elbow

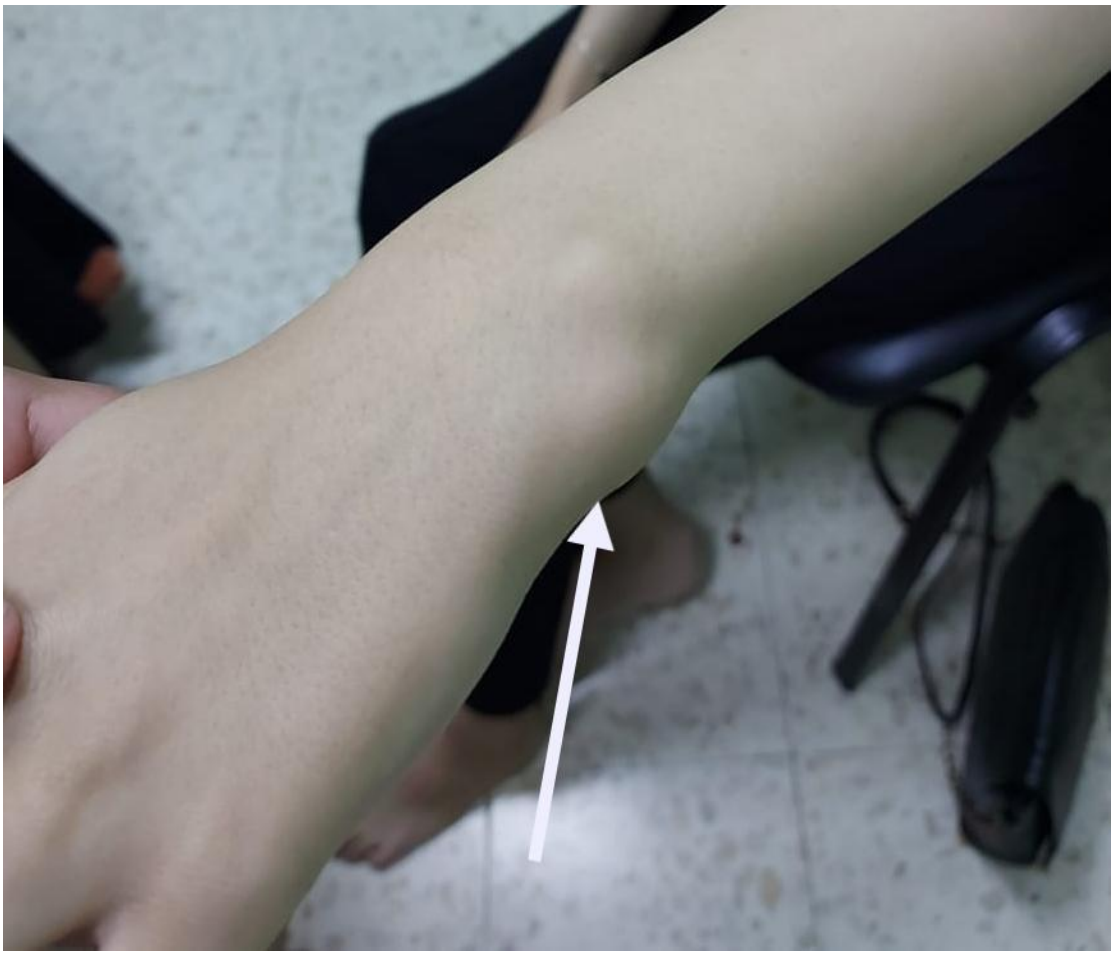

Figure 2(A): Left wrist

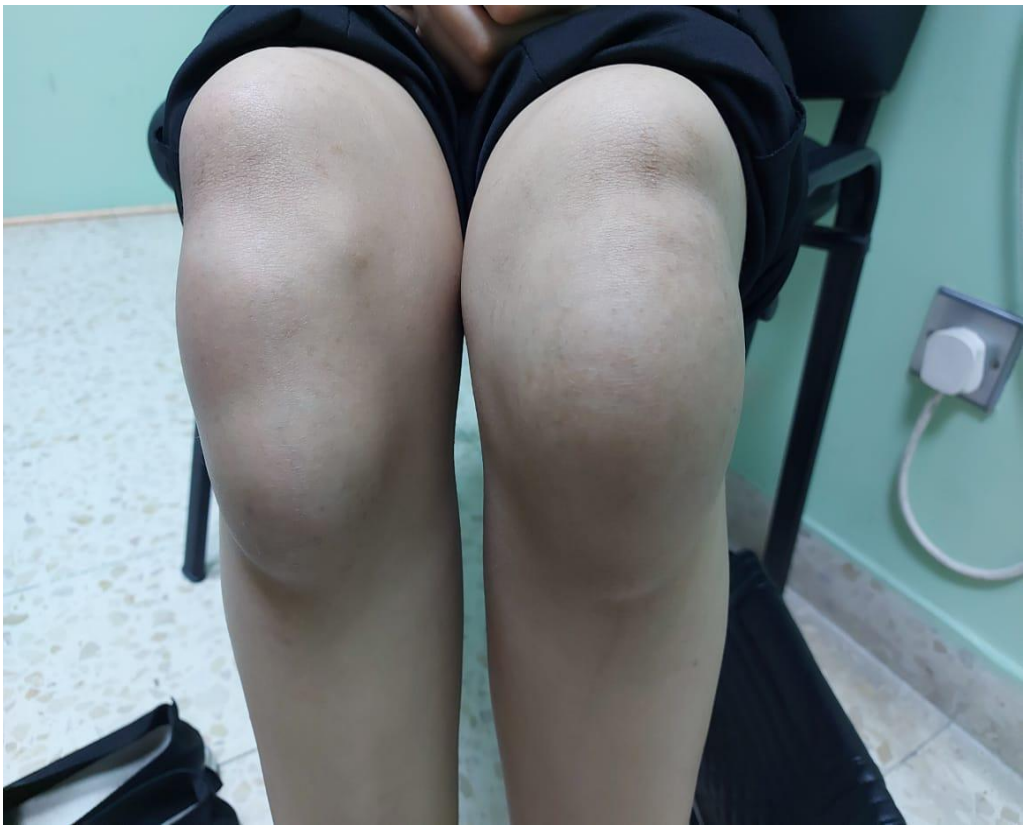

Figure 2(B): Both knees

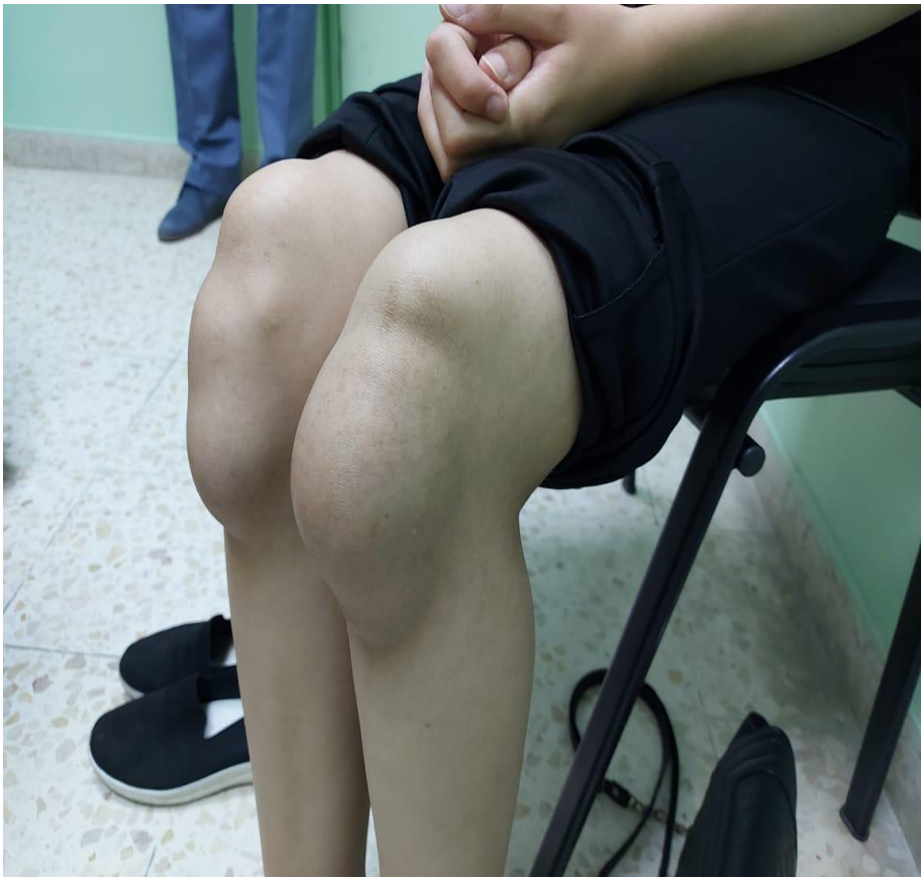

Figure 2(C): Both knees

Laboratory investigations were unremarkable except for hypercholesterolemia; LDL was found to be 17 mmol/l (table 1).

Laboratory (reference range)	Result
CBC	
Hb level (11.5-14)	11.7
WBCs (4000-11000)	7.3 10^3/mm^3
Platelet (150-400) 10^3/mm^3	279 10^3/mm^3
Lipid Panel	
Total cholesterol (0-5.2 mmol/l)	19.55 mmol/l
Triglycerides (0-1.7 mmol/l)	2.57 mmol/l
LDL (0-4.4 mmol/l)	**17.52 mmol/l**
HDL (1.1-1.5 mmol/l)	0.86 mmol/l
Liver Enzymes	
AST (4-44 iu/l)	13 IU/L
ALT (4-44 iu/l)	7 IU/L
Thyroid panel	
TSH (0.3-4.8 µIU/mL)	0.949 µIU/mL
T4 (0.3-4.8 µIU/mL)	13.9
T3 (0.3-4.8 µIU/mL)	4.22
Inflammatory markers	
ESR	**35**
CRP (<5.0)	Negative
Rheumatoid factor	Negative
ACCP	Negative
ANA	Negative

Table 1: Biochemical findings of the presented case

The overall clinical description along with the very high levels of LDL and the presence of lipid-laden histiocytes located in the dermis and subcutis on biopsy (Figure 3) confirmed the diagnosis of tendinous and tuberous xanthomas.

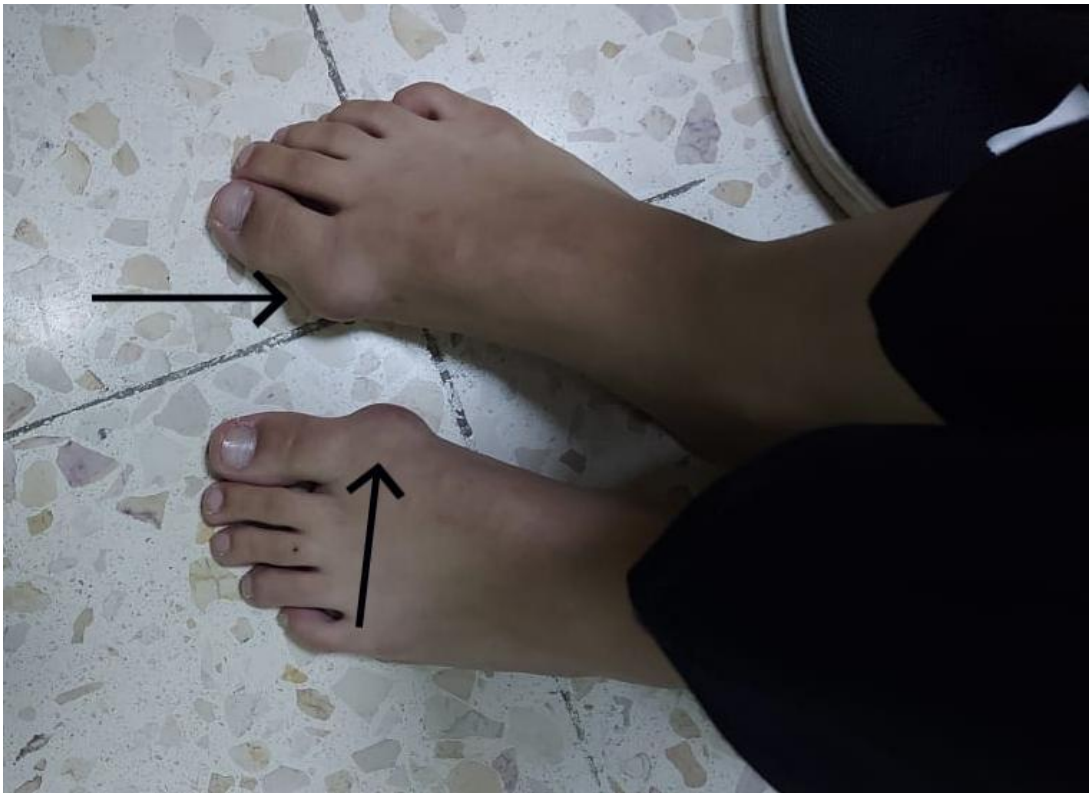

Figure 3(A): Medial aspect of both feet

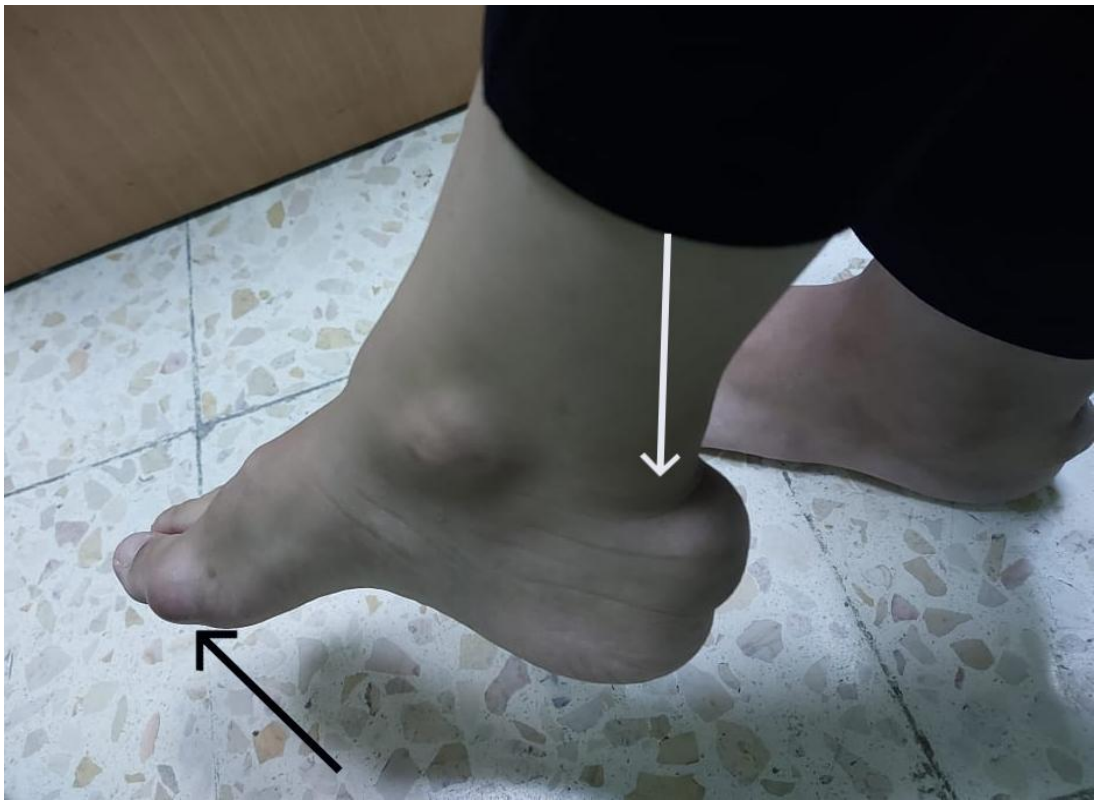

Figure 3(B): Lateral aspect of the foot and Achilles tendon

Subsequently, the diagnosis of familial hypercholesterolemia was made based on high LDL levels, xanthomas, and a family history of early cardiovascular disease and early death. Therefore, the patient has been advised towards lifestyle modification and treatment started with statins with gradual dose increments aiming to reach the highest tolerated dose. The patient was counseled about possible future surgical interventions. Screening lipid profile was recommended to all family members (Figure 4 and 5).

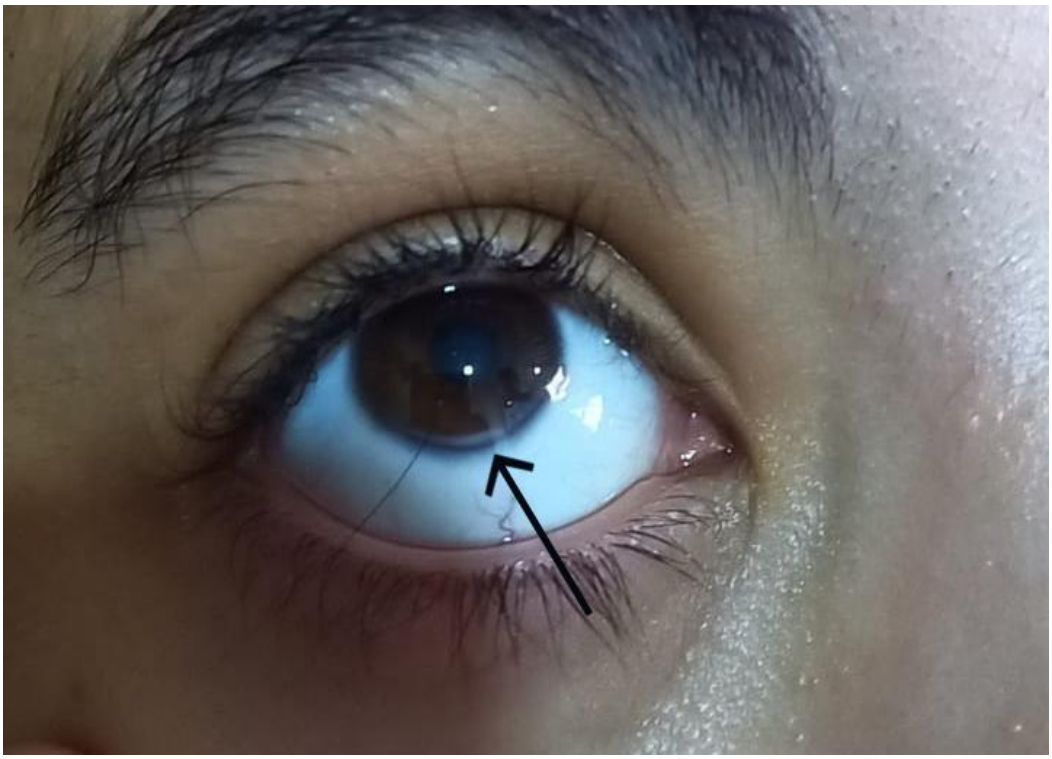

Figure 4: Arcus Lipoides Juvenalis

Figure 5: Histopathology shows lipid-laden histiocytes located in dermis and subcutis

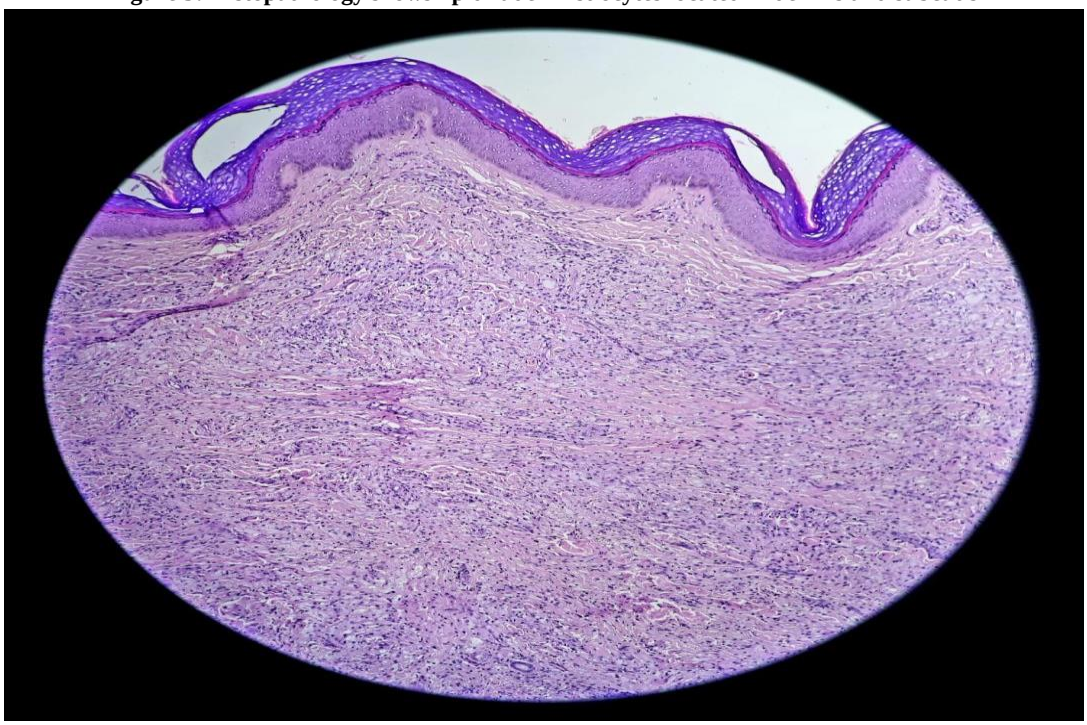

Figure 5(A): Microscopic view lipid-laden histiocytes located in dermis and subcutis

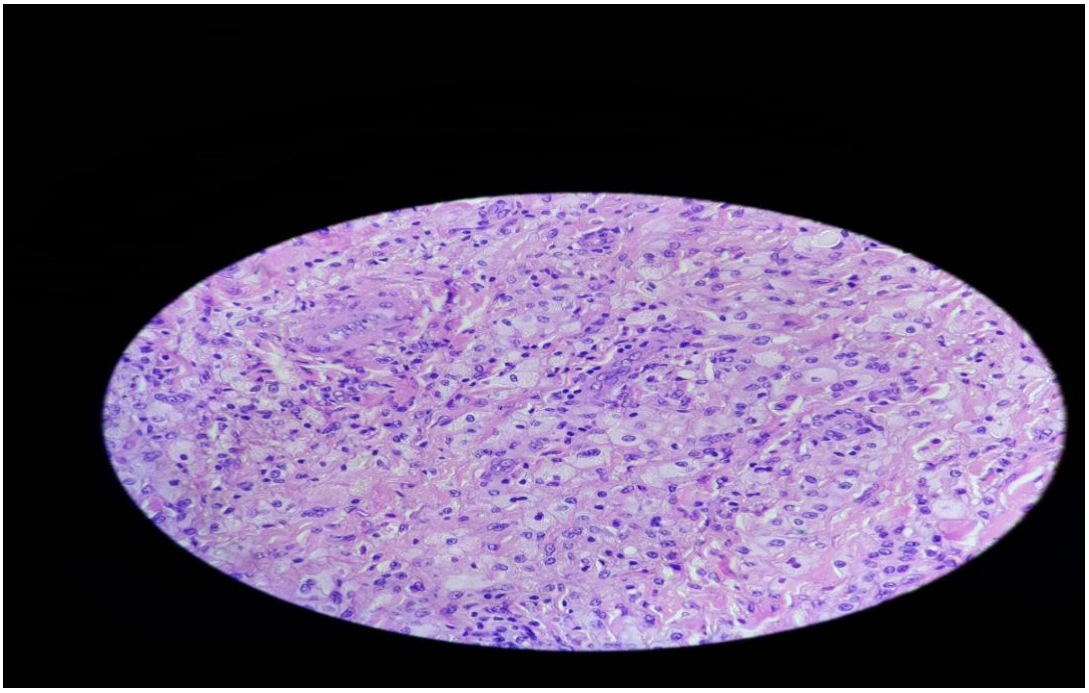

Figure 5(B): Closer view lipid-laden histiocytes located in dermis and subcutis

3. Discussion:

Rheumatoid arthritis (RA) is an inflammatory disease that affects synovial tissues of the peripheral joints, it is characterized by bilateral and symmetrical joint involvement; mainly joints of the hands and feet [23]. Tendons, ligaments, and other extra-articular structures such as the skin, lungs, and kidneys may also be involved in the disease activity [24]. The prevalence of rheumatoid arthritis (RA) is variable and is affected by race, gender, socioeconomic status, and age and it ranges from 0.3%-4%, however; it's reported to be as high as 9.3% among non-Hispanic African American women [24, 25].

Rheumatoid nodules are the most common cutaneous manifestation of rheumatoid arthritis (RA), they may occur at any site including internal body organs but mainly affect areas exposed to repeated pressure and mechanical stress such as the olecranon processes. They are mainly

detected among seropositive patients and are associated with a more severe and aggressive inflammatory process. Multiple nodules have been reported at initial presentation in 7 percent of patients with rheumatoid arthritis (RA) and are found at some time during the disease course in 20 to 40 percent of patients [26, 27]. The accelerated formation of multiple rheumatoid nodules may also occur in association with the use of certain medications, particularly methotrexate [28]. The presence of rheumatoid nodules can infrequently be seen with only mild or no systemic manifestations of RA; a condition termed rheumatoid nodulosis [29].

Some cases of rheumatoid nodules were reported to be misinterpreted as xanthomas, and the other way around [30]. Tendinous xanthomas and rheumatoid nodules share some characteristics that may lead to confusion between the two entities and end with wrong diagnoses and delayed management; the most important of which is their similar distribution over extensor surfaces of the arms and legs, and this was what directed our patient's general practitioner towards a wrong diagnosis of rheumatoid arthritis [31]. Furthermore, the possibility of the presence of cholesterol crystals in both xanthomas and rheumatoid nodules on FNA may add more confusion [32] and necessitate performing a tissue biopsy [33]. It is worth mentioning that both conditions have an increased risk of cardiovascular disease and indicate poor prognosis for the primary disorder [34].

Skin and tendon xanthomas are extremely important manifestations of familial hypercholesterolemia (FH), and their presence is linked to severe early ischemic events [30]. Even in the absence of apparent xanthomas, Achilles' tenosynovitis presenting merely as tendon pain is observed in patients with FH [35]. So, serum cholesterol measurement in young patients presenting with a painful Achilles tendon is mandatory as it could allow early diagnosis of FH [36].

Management of xanthomas starts with the early diagnosis especially when it is associated with familial hypercholesterolemia. Successful Surgical resection of large xanthomas in conjugation with aggressive lipid-lowering therapy has been reported, but not as monotherapy [37].

Gradual escalation of lipid-lowering therapy should always be taken into account, and exacerbations of Achilles tendinopathy should be anticipated; it is attributable to the effect of statins in lowering cholesterol levels rapidly, this is similar to the worsening of rheumatoid nodules when commencing treatment for RA [38].

Based on our patient's clinical presentation including the absence of significant signs of inflammatory arthritis and the positive family history of premature coronary artery disease, along with her negative inflammatory markers, very high titers of LDL level, and the true cut biopsy results confirming xanthomas; a diagnosis of familial hypercholesterolemia has been made and she has been started on statin therapy and ezeteimibe with gradual dose increments and regular endocrinology follow up, Endocrinology team decided to start novel lipid-lowering agent like evolocumab.

4. Conclusion:

The case report emphasizes that Xanthomas should be considered within the differential diagnoses for any multiple skin nodules, as it can be easily supported by performing simple noninvasive blood tests (Lipid panel). It also highlights the importance of attaining a histopathology diagnosis for ambiguous cutaneous lesions before proceeding with any treatment and not only relying on clinical diagnosis.

5. Declarations:

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part, after obtaining consent form patient's parent.

Patient Consent Form: The patient and her family were consented and informed about subject of the study.

Conflicts of interest: There are no conflicts of interest.

Financial support and sponsorship: None.

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