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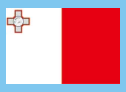

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MINIREVIEWS

# Skin-gut axis: The relationship between intestinal bacteria and skin health

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## Abstract

The gut microbiome is an emerging area of interest in medicine. Imbalances in the gut microbiome have been linked to a number of disease states such as obesity and type 2 diabetes. The relationship between normally residing intestinal bacteria (the *gut microbiota*) and their potential role in the pathogenesis of skin diseases is an area of research for which we are only beginning to understand. Small studies have demonstrated underlying changes in the gut microbiome of patients with certain dermatological diseases. Interestingly, studies suggest that probiotics may have a role in the treatment of atopic dermatitis. However, the concept of the "skin-gut axis" is a newly emerging and important avenue of investigation, still lacking in pathobiological explanations. This review will introduce and describe the intestinal microbiome as it relates to skin health in a complex communication network between the immune system, endocrine system, metabolic system, and nervous system.

**Key words:** Gut microbiome; Skin; Bacteria; Probiotics; Dermatology



**Core tip:** The intestinal microbiome is a complex and dynamic bacterial community that plays an important role in human health. Alterations in microbiota composition have been related to different intestinal and extra-intestinal diseases such as psoriasis and rosacea. Studies have reported beneficial interactions between the human body and its microbiota and modulation through prebiotics and probiotics may prevent or resolve such diseases. Although the mechanisms for how the gut and skin communicate are not fully understood the association likely involves a complex connection between the nervous, immune, and endocrine systems as well as environmental factors.

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## INTRODUCTION

The role of the gut microbiome as an important determinant of human health and disease has emerged as an exciting niche of research in many areas of medicine. An imbalance in the gut microbiome has been linked to obesity, type 2 diabetes, atopy and inflammatory bowel disease (IBD)[1]. Furthermore, the relationship between normally residing intestinal bacteria (the *gut microbiota*) and their potential role in the pathogenesis of skin diseases is an area of research for which we are only now starting to gain an understanding. The small and large intestines provide residence for a vast community of bacteria and their metabolites and by-products, which we call the *gut microbiome*. Similarly, thousands of microbial organisms and their by-products inhabit the skin, referred to as the *skin microbiome.* In both the gut and the skin, a harmonial balance in these microflora is important in maintaining homeostasis[2]. The skin and the gut have more similarities than one would suppose, and in fact, there is budding interest in learning how the skin and gut communicate and influence the health of one another[3]. Both contain rich vascular supply, diverse microbial communities, and act as vital interfaces between the internal human body and the external environment. Additionally, the skin and gut both operate as neuro-immuno-endocrine organs, and participate in essential communication with the nervous system, immune system, and endocrine system. The "brain-gut axis" has been documented extensively in the literature, and was first described in 1930 when Stokes and Pillsbury attributed depression to altering the gut microbiome, leading to inflammatory skin diseases[4]. However, the "skin-gut axis" is a newly emerging and important avenue of investigation, still sparse in pathobiological explanations. This review will introduce and describe the intestinal microbiome as it relates to skin health in a complex communication network between the immune system, endocrine system, metabolic system, and nervous system.

## HUMAN INTESTINAL MICROBIOME

The "gut microbiome" refers to the diverse community of microbial organisms that normally inhabit the bowel and their metabolites/byproducts[5]. There are more than 100 trillion bacteria present in the human gastrointestinal tract, consisting of over one thousand different species colonizing the intestines[6,7]. A large proportion of the organisms found in the gut microbiome belong to two phyla: *Firmicutes* and *Bacteroidetes*[5]. The density of the bacterial populations within the bowel differs by anatomical location. For instance, the density is approximately $10^{2-3}$ colony forming units (CFU) per gram in the proximal ileum and jejunum, compared to the ascending colon which has approximately $10^{11-12}$ CFU per gram[8]. There is significant variation in the gut microbiome communities among healthy individuals[9]. The gut microbiome is relatively stable, however, studies have demonstrated that antibiotic therapy, international travel, and illness can all alter the normal gut microbiome. Aging can also lead to a shift in the predominant species within the gut microbiome. Research currently suggests that our long-term dietary patterns could have a large impact on the composition of our gut microbiome[6].

The role of the gut microbiome is thought to include proper development and functioning of the immune system, protection against infections, digestion of polysaccharides, and synthesis of vitamins[7]. The symbiotic relationship between resident gut bacterial flora and the host is vital to the normal immune system development and homeostasis of the host and regulation of epithelial growth and differentiation[10].

## PROBIOTICS/PREBIOTICS

Probiotic supplementation has become increasingly popular, with many commercially available products in capsule, powder, beverage, and food forms. According to the Food and Agricultural Organization of the United Nations and the World Health Organization, probiotics are considered to be "live microorganisms which when administered in adequate amounts confer a health benefit on the host"[11]. The most frequently used bacteria are from the *Lactobacillus* and *Bifidobacterium* genera[12]. There has been evidence to suggest that they are useful in the treatment of irritable bowel syndrome (IBS), diarrhea, and lactose intolerance[13]. Probiotics may alleviate abnormal alterations of the gut microbiome, referred to as "dysbiosis". Dysbiosis of the gut microbiome has been linked to metabolic disorders, gastrointestinal infections, IBD, and irritable bowel syndrome (IBS)[14]. Probiotics are thought to provide therapeutic benefits *via* multiple mechanisms. Firstly they are believed to prevent pathogenic bacteria from colonizing the gastrointestinal tract, which would otherwise subsequently lead to disease. Secondly, they are thought to improve the barrier function of the colonic mucosa. Thirdly, probiotics may help modulate the immune system, which may help shift away from pro-inflammatory immune reactivity[12]. Fourth, they may synthesize and secrete metabolites that may have nutritional benefits and anti-inflammatory effects[15]. Lastly, probiotics may even play a role in modulating central nervous system and enteric nervous system functions. In fact, in a randomized controlled trial patients with Alzheimer's disease who received probiotic supplementation for 12 wk had significant improvement in mental status score and had a significant decrease in serum c-reactive protein (Akbari, 2016 #991). Additionally, probiotic supplementation has demonstrated

improvement in multiple sclerosis symptoms and exacerbations (Dolan, 2016 #992).

Probiotics have not yet been widely studied in the treatment of dermatological diseases. Two meta-analyses failed to demonstrate any clinically significant changes in the severity of atopic dermatitis (AD) in children treated with probiotic supplementation[16,17]. However, Lee *et al*[16] found a significant risk reduction (up to 61%) of pediatric AD in those who were treated with prenatal and/or postnatal probiotics. There are even fewer studies available regarding the treatment of adults with AD using probiotics. These small studies have demonstrated that there may be a clinical benefit in adults[18-20]; however, larger trials are needed before any conclusions can be drawn. Probiotics are postulated to help in atopic dermatitis by improving the diversity of the intestinal flora, increase the barrier function of the skin and mucosa and by producing a mainly Th1 response[13].

Prebiotics are non-digestible carbohydrates that help stimulate the growth of certain bacteria in the gut, which can lead to an improvement in the health of the host[21]. A review by Osborn *et al*[22] of four clinical trials found that there was a statistically significant reduction in the incidence of infant eczema with prebiotic supplementation of galactoligosaccharides and fructooligosaccharides (RR 0.68). It has been demonstrated that milk glycoproteins are able to select for and stimulate the growth of *Bifidobacteria longum infantis (B. infantis)* in the gut microbiome[23]. This is of clinical importance as *B. infantis* supplementation can reduce the risk of necrotizing enterocolitis in preterm infants. *B. infantis* colonization of the gastrointestinal tract is associated with improved immune response to vaccination and weight gain[24].

However, further studies need to be conducted into the use of prebiotics and probiotics before recommendations regarding their use in the treatment or prevention of dermatological diseases can be made.

## LINK BETWEEN SKIN DISEASE AND THE GUT

Gastrointestinal disorders can present with dermatological skin findings. IBD is linked to skin manifestations such as pyoderma gangrenosum, erythema nodosum, Sweets Syndrome and oral lesions[23]. Celiac disease is associated skin manifestations such as dermatitis herpetiformis, alopecia, vitiligo and oral mucosal lesions. Furthermore, psoriasis is more commonly found in patients with Crohn's disease than healthy people[24].

There is emerging evidence linking certain dermatological disorders to gut dysbiosis. However, this is not a novel topic and in fact, in 1911 a gastroenterologist named Milton H. Mack wrote, "Acne and eczema are both traceable to this fountainhead of diseases… if in a case of urticarial we look to the intestinal track, why not in eczema and acne?" [25]. Simultaneous gut and skin microbiome dysbiosis has been observed in several inflammatory skin diseases, such as rosacea, psoriasis, and atopic dermatitis[26].

### *Psoriasis*

Interestingly, patients with psoriatic arthritis are at increased risk of developing IBD and have subclinical evidence of gut inflammation[27]. A recent clinical study including 16 patients with psoriatic arthritis, 15 with psoriasis and 17 healthy controls analysed the gut microbiome across these three groups. The gut microbiome was less diverse in the psoriasis and psoriatic arthritis groups; with a decrease in the *Coprococcus* spp. Those with psoriatic arthritis experienced a reduction in important bacterial enterotypes such as *Akkermansia, Ruminococcus, and Pseudobutyrivibrio*. It is thought that these taxanomic changes cause to a reduction in the ability of the gut to regulate immune responses, which may lead to systemic or localized inflammation[28].

In addition, a clinical trial has shown that treating psoriasis patients with probiotic *Bifidobacterium infantis* 35624 for eight weeks improved C-reactive protein (CRP), TNF-alpha and IL-6 levels. However, during this study no clinical assessments were performed after baseline. These results suggest that probiotic supplementation could modulate inflammation in this disorder[29].

### *Rosacea*

Rosacea has been linked to *Helicobacter pylori* (*H. pylori*) infection, however the efficacy of *H. pylori* eradication in rosacea therapy is unclear[30]. Moreover, a study of 113 rosacea patients demonstrated that those with rosacea have a higher incidence of small intestinal bacterial overgrowth (SIBO) when compared to controls. Those with SIBO were treated with either rifaximin therapy for 10 d or placebo. Those who were treated with antibiotic therapy experienced an improvement in their symptoms for at least nine months[31].

### *Atopic dermatitis*

There is a well-documented association between gut microbiome dysbioses and low diversity within the gut microbiota with the development of allergic diseases (Melli, 2016 #993). Conversely, increased microbial diversity within the gut has been associated with reduced flares in inflammatory skin diseases, such as atopic dermatitis (Marrs, 2016 #994).

## PROPOSED MECHANISMS REGARDING THE SKIN-GUT AXIS

At present, there is clinical evidence suggesting a close relationship between intestinal dysbiosis and dermatologic conditions. However, the mechanistic basis behind these observations has yet to be confirmed. The association between the gut and skin likely involves a complex and multifactorial interplay between the

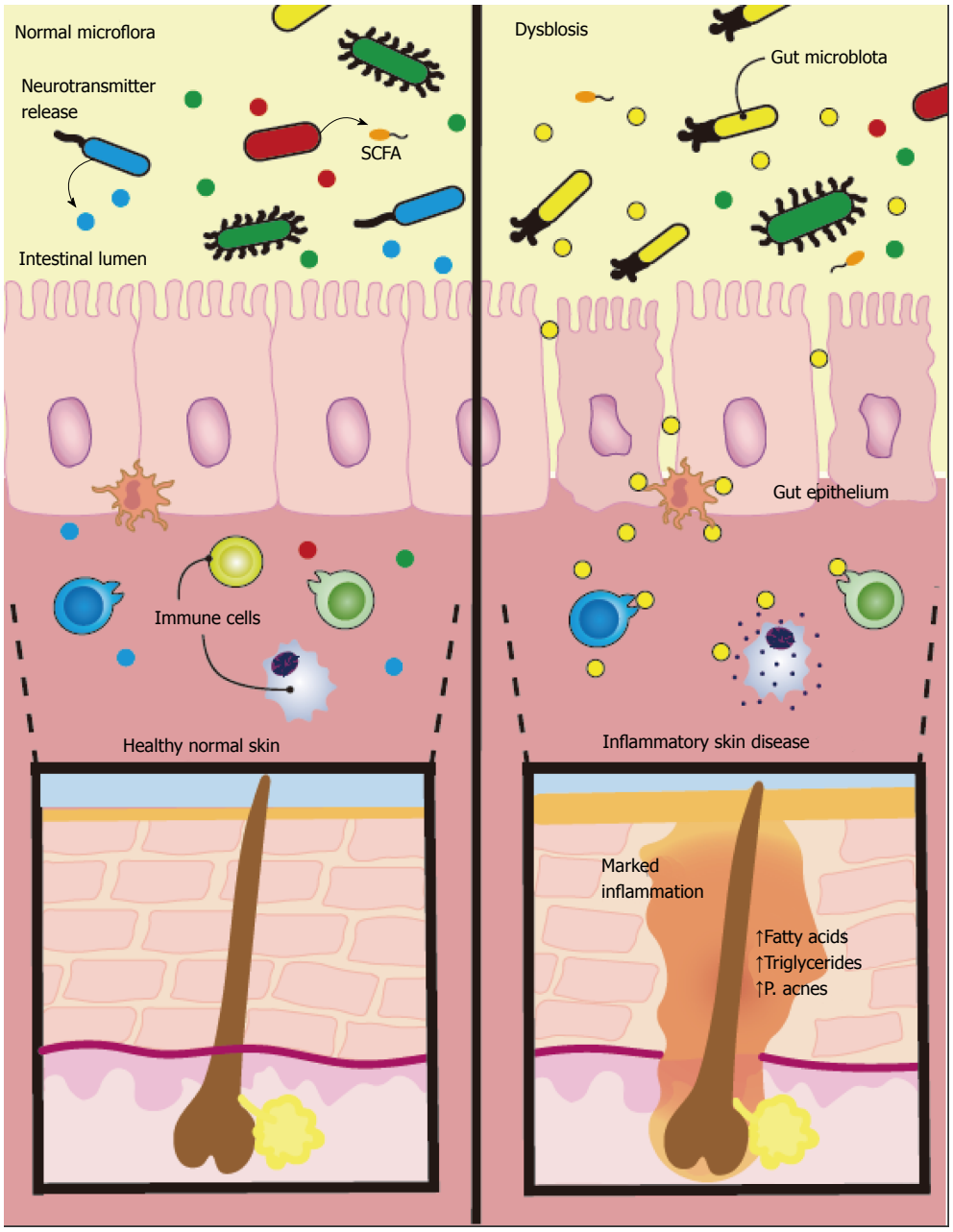


**Figure 1 There is emerging evidence linking dermatological disorders to alterations in gut bacteria.** Studies hypothesize intestinal flora produce neurotransmitters in response to stress that can modulate skin function. These neurotransmitters cross the intestinal epithelium enter the bloodstream and induce systemic effects. Along with neurotransmitters, the gut microflora also release short chain fatty acids (SCFAs), which can also enter systemic circulation and affect the skin. Additionally, diet may influence inflammation in the skin though nutrient signalling and release of long chain fatty acids, leading to excessive stimulation of sterol regulatory element-binding protein 1 and increased synthesis of fatty acids and triglycerides promoting *Propionibacterium acnes* overgrowth.

nervous, immune, and endocrine systems as well as environmental factors such as diet and medications (Figure 1).

### *Skin-gut axis and the neuroendocrine system*

The "brain-gut-skin axis" has been eloquently documented by Arck *et al*[32] and Bowe and Logan[4]. It is known that psychosocial stress is implicated in both exacerbation and the initiation of various skin conditions[33]. It is plausible that the intestinal microflora produce neurotransmitters in response to stress and other external stimuli that could modulate skin function *via* neural pathways. For instance, commensal organisms in the gut can produce norepinephrine, serotonin, and acetylcholine or may evoke the release of neuropeptides from nearby enteroendocrine cells[34]. These neurotransmitters might cross the intestinal epithelium into the bloodstream and induce systemic effects[35]. Along with neurotransmitters, the gut microflora also release short chain fatty acids (SCFAs), including propionic acid, butyric acid, acetic acid, and lactic acid derived from polysaccharide fermentation from food we eat[36]. The majority of these SCFAs are produced in the large intestine, where the colon is highly efficient in the reabsorption of fatty acids, only allowing approximately

10% to remain in expelled feces[37]. The true systemic levels of SCFA derived from the colon depend on individual dietary habits, rate of SCFA production by gut microbes, and the degree of absorption through the large intestine. It is not known whether these metabolites, along with many others produced by gut microbes, are able to reach clinically significant levels in the bloodstream in order to impact the skin[38].

### *Immune system modulation*

Health, including skin health and overall well being, require tightly integrated immune and hormone feedback systems that allow beneficial microbial to dominate in the gut and on the skin[39]. The normal gut microbial residents continuously interact with the immune system to support host homeostasis. In general, immune system homeostasis requires a proper balance of pro-inflammatory and anti-inflammatory signals and molecules in response to internal and external environmental changes. If the microbiome composition changes for any given reason, the immune system reactivity could subsequently shift and eventually lead to inflammatory skin diseases[40]. This idea was exemplified in a mouse study by Zanvit *et al* which demonstrated that mice treated with antibiotics neonatally had exacerbated imiquimod-induced psoriasis as an adult, while mice treated with the same antibiotics in adulthood had improved psoriasis (Zanvit, 2015 #990). This study demonstrates the importance of how neonatal gut dysbioses can affect skin inflammation, potentially triggering or exacerbating inflammatory skin diseases such as psoriasis later in adulthood. Interleukin-10 (IL-10) is generally considered to decrease pro-inflammatory molecules, such as IL-17[41]. Animal models have shown that probiotic supplementation up regulates IL-10 and provides beneficial skin effects[42]. In a recent article, Zákostelská *et al*[43] hypothesize that certain beneficial families of intestinal bacteria, such as lactobacilli, are able to supress the IL-23/Th17 axis, which is believed to play an important role in inflammation involved in psoriasis[43]. This suppression may occur through certain gut commensal organisms' ability to down regulate IL-23 and transforming growth factor-beta (TGF-β) expression, and preventing Th17 cell-mediated release of proinflammatory IL-17[44]. As a result of immune system dysfunction and deficiency in T regulatory cells, some autoimmune diseases can result in rampant inflammation and severe dermatitis, such as in IPEX syndrome (Halabi-Tawil, 2009 #996). The intestinal microbiome is responsible for regulating the expansion of T regulatory cells, Th1 and Th2 type cells to provide immune system homeostasis, and there has been recent research investigating how treating the gut microbiome could improve these types of skin conditions (He, 2017 #995). These are examples demonstrating the complex interplay between the immune system and gut commensal organisms. The true connection between skin health and gut bacteria induced immune system reactivity is poorly understood and still requires more extensive investigation.

### *Diet*

Recent research continues to reveal the influence of the "western diet" in the obesity epidemic, and researchers have hypothesized that alterations in the gut microbiome due to high dietary fat intake could be partly to blame (Murphy, 2015 #997). In the literature, it is generally accepted that high fat diets lead to gut dysbioses, reflected by a decrease in *Bacteroidetes* species and an increase in *Firmicutes* species (Zhang, 2012 #998). Although the exact mechanisms are still under investigation, "western diet" induced gut dysbioses may be associated with cancer (Schulz, 2014 #999), atherosclerosis and heart disease (Gregory, 2015 #1000), insulin resistance (Carvalho, 2012 #1001), and even disorders of the central nervous system (Scheperjans, 2015 #1002). Until recently, conflicting opinions and inconclusive evidence have predominated regarding the link between diet and skin conditions. Although more mechanistic studies are warranted, there is growing evidence that diet plays an important role in the pathogenesis of skin diseases, with acne vulgaris being an example. For example, the western diet consisting of large amounts of saturated fats and high glycemic load has been strongly associated with acne[45,46]. Researchers hypothesize this occurs from problems in nutrient signalling, ultimately leading to excessive stimulation of sterol regulatory element-binding protein 1 (SREBP-1) and increased synthesis of fatty acids (ex - free oleic acid) and triglycerides in sebum that promotes flourishing *Propionibacterium acnes* growth[47]. The strong association between atopic dermatitis and food sensitivities similarly exemplifies the importance of food on the gut-skin relationship[48]. The ability of diet to both positively and negatively influence skin function demonstrates the undeniable link between the skin and gut, however, the mechanisms surrounding this connection is likely multifactorial and at present based primarily on theory. Indeed, it is difficult to detangle the direct effects of food on the skin versus food's modulation of the intestinal microflora.

## CONCLUSION

The intimate relationship between the gut and skin is undeniable. Possibly, both the intestinal bacteria themselves and their metabolic by-products influence skin physiology. The mechanisms are still under study but there are a few theories: (1) bacterial products and diet could alter the physiology of the gut epithelium, resulting in different secretory products that might circulate systemically and reach the skin; (2) neurotransmitters, hormones, and other bioactive chemicals such as SCFAs derived from the gut could all act on receptors within the skin and directly alter the skin or alter the skin's commensal bacteria; and (3) ingested compounds and chemicals may absorb and have a direct effect on the skin's appearance or function[49].

Although not a new avenue of research, the relationship between the gut microbiome and skin health is emerging as an important and intriguing topic in dermatology and gastroenterology alike. It is especially important to understand how diet, medications, and psychosocial stress can influence or contribute to altered microbial communities in the gut, which may directly or indirectly affect skin health.

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CASE REPORT

# Pleomorphic cutaneous xanthomas disclosing homozygous familial hypercholesterolemia

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Author contributions: Mastrolorenzo A and D'Errico A designed the report; Pierotti P performed the infectivology analyses; Mastrolorenzo A and D'Errico A collected the patient's clinical data; Giannini S and Fossi F perfomed the vascular and metabolic analyses, dyspipidemia management and critical revision; Vannucchi M perfomed the histopathological analyses; Mastrolorenzo A and D'Errico A analyzed the data and wrote the paper.

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Informed consent statement: The patient involved in this case report has signed an informed consent allowing the use of pictures and information in an anonymous format.

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## Abstract

Homoxygous Familial Hypercholesterolemia is characterized by a presence of several types of cutaneous xanthomas with an abnormal lipid profile. Some of these could be pathognomonic. Although these could be initially interpreted as isolated and localized benign disorders and offered surgical treatment, it has become increasingly clear that they could be a part of a systemic pathology. Here we describe a case of this rare disorder in a 19 years old non-obese young man who presented multiple, intertriginous, tuberous and tendinous xanthomas and had an associated abnormal lipid profile with elevated low-density lipoprotein cholesterol levels. A detailed history with clinical assessment in the differential diagnosis and laboratory investigations led to a precise diagnosis.

**Key words:** Intertriginous xanthomas Homoxygous Familial

Hypercholesterolemia; Familial hypercholesterolemia; Dyslipidemia; Xanthomas



**Core tip:** This article describes a contemporary approach to the differential diagnosis of xanthomas, and the morphological classification from a review of the literature, specifically reflect the clinical findings evidenced in this case report.

Mastrolorenzo A, D'Errico A, Pierotti P, Vannucchi M, Giannini S, Fossi F. Pleomorphic cutaneous xanthomas disclosing homozygous familial hypercholesterolemia. *World J Dermatol* 2017; 6(4): 59-65 Available from: URL: http://www.wjgnet.com/2218-6190/full/v6/i4/59.htm DOI: http://dx.doi.org/10.5314/wjd.v6.i4.59

## INTRODUCTION

The clinical picture of xanthomas is variable from yellow or orange dermal macules or papules, to soft or firm-hard subcutaneous plaques and tendinous nodules not attached to underlying structures, with normal-appearing overlying skin. In recent years, interest in xanthomas has been growing for several reasons, mainly because the pathogenetic mechanisms involved in the development seems to be similar to those in early stages of atherosclerotic plaques[1]. Cholesterol accumulation in tissues produces common dermatological manifestations as several types of cutaneous xanthomas[2]. The association of xanthomas with lipoprotein disorders was initially defined by Frederickson's classification[3,4]. From that phenotypic classification the recent advances in molecular genetics led to the discovery of a broad group of disorders of the lipids metabolism disclosing the relationship between the development of xanthomas and hyperlipidemias[1,5,6].

Xanthomas can be classified following clinical as well as patho-anatomical schemes, addressing special attention to the needs of dermatologists and internal medicine specialists respectively. These correlated issues gave rise to the following groups which are useful in clinical practice: Normolipidaemic xanthomas (NX), hyperlipidaemic xanthomas (HX), and necrobiotic xanthogranuloma (NXG)[1,7,8]. Nevertheless, xanthomas may be seen either as a primary disorder (primary dyslipidemia, an inherited abnormality of lipoprotein metabolism) or secondary disorder (hyperlipidemia secondary to systemic disease or medication)[1,4,9].

Cutaneous xanthomas may or may not be present with lipid metabolic disorders, usually depending on the severity of the lipid abnormality. Normolipidemic xanthomas mostly appear as diffuse flat skin lesions, while hyperlipidaemic types are polymorphous, often tuberous, and can affect either skin or tendons and joints. Recognition of these types of xanthomas may be facilitated on the basis of clinical morphology, presence or absence of inflammation, anatomic distribution, and development pattern, defining the primary type of lesion and histologic level of involvement. From a dermatological point of view these can be categorized in two specific subsets and each one with distinctive clinical associated features: (1) papulonodular xanthomas: Eruptive and tubero-eruptive xanthoma, xanthoma tuberosum (the term "tuberous" refers to the nodular character of these xanthomas) and tendineum; and (2) plane xanthomas: Plane and intertriginous xanthoma, striated palmar xanthoma and xanthelasma palpebrarum[1,4,9-11].

We report a case of a young man with multiple pleomorphic cutaneous xanthomas in association with a neglected Homoxygous Familial Hypercholesterolemia (HoFH). This article thus presents a contemporary approach to the differential diagnosis of xanthomas, and the diagnostic criteria we propose was developed after a review of the literature, and reflect the clinical findings evidenced in our patient, seen at our dermatological facility.

## CASE REPORT

A 19 years old non-obese young man presented as an outpatient to our hospital with multiple, bilateral and symmetrical slow growing yellowish lesions of various forms over the dorsum of the elbows, knees, buttocks, ears, feet and hands. Biopsy of three representative and different skin lesions revealed them to be xanthomas characterized by the presence in the dermis of cholesterol crystalline aggregates surrounded by fibrosis and foamy cells (Figure 1).

On dermatological examination each lesion was defined on morphological pattern. The following clinical forms have been recognized: (1) Xanthelasma: Involving the inner canthus of the left eye (Figure 2); (2) Intertriginous xanthomas and a confluence of plane-eruptive xanthomas (Figure 3): In finger web spaces (Figure 3A), toe web spaces (Figure 3C and D), and the flexural surfaces: the ankle crease (Figure 3D), the antecubital fossae (Figure 3E and F), the popliteal fossae (Figure 3G and H) and the creases of ears (Figure 3I and J); (3) Tendinous xanthomas (Figure 4): To form a single mass localized all over the Achilles tendon just above its insertion point to the calcaneal tuberosity; and (4) Tuberous xanthomas (Figure 5): Soft skin color or yellowish nodules and tumors, with a tendency to coalesce, localized on the knees (Figure 5A and B), malleolus (Figure 5C) and buttocks (Figure 5D).

The lesions appeared at about 2 years of age on both lateral malleolus, at 3 years of age over the buttocks; they were originally asymptomatic then progressively increased in size and extent. At present time the size of the lesions varied between 1 cm × 1 cm × 1 cm to 10 cm × 5 cm (over the Achilles tendon, Figure 4) and 10 cm × 10 cm (over the buttocks, Figure 5D). On detailed clinical history the patient had symptoms of discomfort and pain in the elbows for bilateral massive

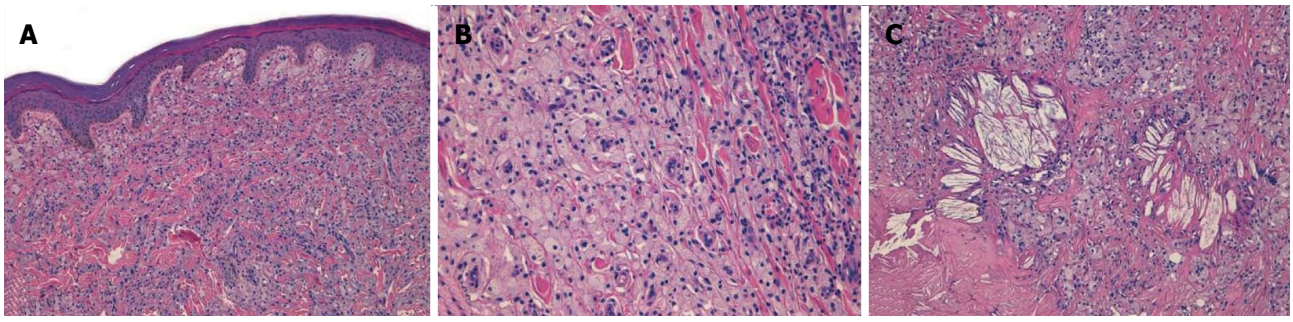


**Figure 1 Histopathological examination.** A: Foam cells infiltrate the superficial and deep dermis in cluster, separated by collagen fibers. Absence of any other significant inflammatory infiltrate (10 ×, EE); B: Xanthoma cells are filled with optically empty vacuoles, showing thin, well defined cytoplasmic membranes, and tend to be attached to each other. They can be multinucleate (20 ×, EE); C: Presence in the dermis of cholesterol crystalline aggregates surrounded by fibrosis and foamy cells (10 ×, EE).

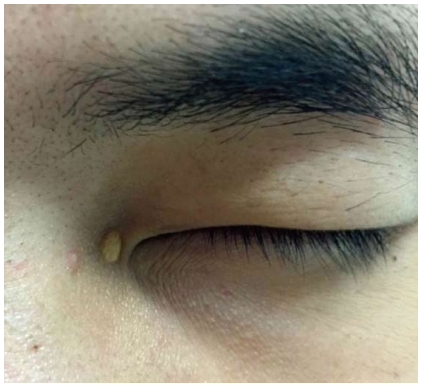

**Figure 2 Xanthelasma.** Single yellow-orange papular lesion on the inner canthus of the eye.

tuberous xanthomas and at the age of 8, for significantly restricted joint mobility at these sites he had surgery in China in a rural hospital. Up to day the removed lesions did not recur (Figure 6). However, the discomfort and pain due to the large size of the masses of the buttocks and the limitation of his walking distance for the Achilles tendinous xanthomas progressively worsened resulting in significant disability.

Clinical examination did not reveal xanthomatous infiltration of cornea, oral, pharyngeal, and laryngeal mucosae. The patient's family history was remarkable in that both nonconsanguineous parents had a chronic hepatitis B and high total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels. The 17 years old sister had a mild hypercholesterolemia, but no other family members have shown any other inherited disorders and such similar xanthomas. The patient's plasma TC level in the last six months ranged between 657 mg/dL and 990 mg/dL (reference value < 200), and LDL-C level was 557 mg/dL (reference value < 130). Triglycerides and high density lipoprotein cholesterol (HDL-C) levels were normal. Although not useful for the diagnosis or for clinical purposes, we also measured the plasma levels of other lipoproteins in order to better quantify the lipid profile of the patient. In particular plasma levels of apolipoprotein (Apo) A1 was normal, while the level of ApoB 345 mg/dL (reference value 55-140) and atherogenic lipoprotein (aLp) 734 mg/dL (reference value < 300) were increased.

Blood pressure was 16/11 kPa. Renal function tests, hemogram, thyroid function tests, immunoglobulins, erythrocyte sedimentation rate were all normal. The patient was suffering of a chronic hepatitis B with no current liver damage. He received a first course of entecavir therapy 0.5 mg once a day for the last 10 mo because he was tested positive for the hepatitis B "s" antigen (HBsAg), fluctuating or minimally elevated liver enzymes [alanine transaminase (ALT) 118 IU/L (reference value < 50) and aspartate transaminase (AST) 62 IU/L (reference value < 50) and very high viral load (real time HBV DNA 158000000 IU/mL)]. The patient was referred to our STDs Centre in order to establish if the dermatologic disorder was HBV-related. New test results for liver enzymes, HBV DNA, and sonography of the liver were negative.

Abdomino-pelvic ultrasonography, chest X-ray, brain magnetic resonance imaging and upper and lower gastrointestinal endoscopy revealed no abnormality. No osseous pathology was noted on plain radiographs.

The patient was referred to the Metabolic Disease Centre of the University of Florence, Centre for dys-lipidemia management. Echocardiography was normal. However, a transoesophageal echocardiogram revealed mild supravalvular aortic narrowing and a luminal irregularity of arch. The artery doppler ultrasound scan showed that the right carotid artery had the intima media 1.5 cm thick, and the right common femoral artery had formed atherosclerotic noncalcified plaques lesions and the intima media was 2.2 cm thick.

Based on the following findings including clinical picture, patient's clinical history, clinical conditions still present in his family, and pathological and serological analysis the patient was diagnosed with HoFH and multiple xanthomas.

At this time the patient is treated with a combined treatment regimen of atorvastatin (20 mg/d), ezetimibe (10 mg/d), a low dose aspirin (100 mg/d) and LDL-C apheresis therapy every two weeks while on the list for

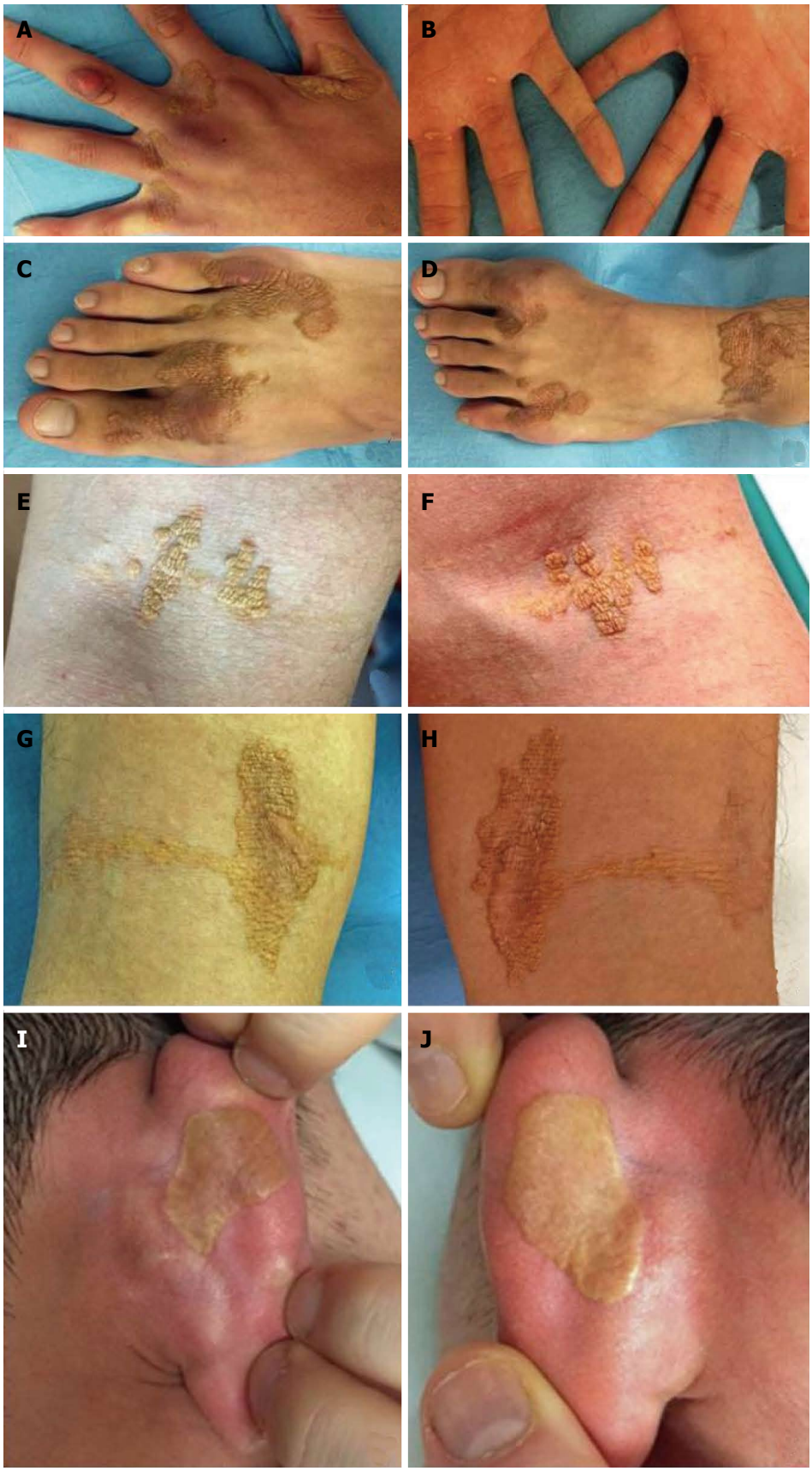


**Figure 3 Diffuse intertriginous xanthomas.** Usually appear in a symmetric distribution as well-demarcated and slightly elevated noninflammatory plaques of ochre-yellow or yellow-brown discoloration. Typically found in intertriginous and flexural areas. A: In finger web spaces, and in this picture with metacarpophalangeal joint tendon xanthoma; B: At metacarpophalangeal palmar crease in linear band or single papules; C: Toe web spaces; D: In toe web spaces and ankle crease; E and F: At antecubital fossae, with the "eruptive" appearance of crops of yellow dermal soft, velvety papules; G and H: In popliteal fossae; I and J: At the creases of ears in a rare pattern of "plane xanthoma" as very thin flat patches, easily clinically missed, of yellow-orange macular discoloration.

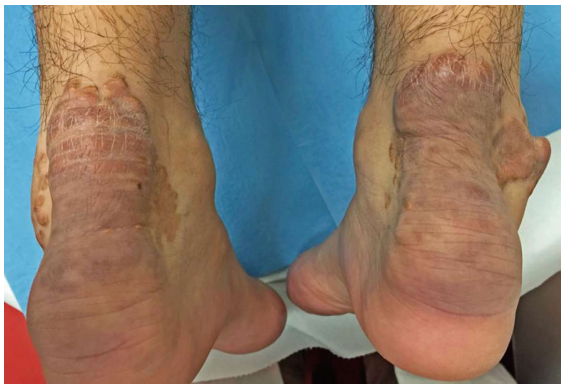

**Figure 4 Tendinous xanthomas.** Bilateral Xanthomas of Achilles tendon. Each swelling was localized all over the tendon just above its insertion point to the calcaneal tuberosity. They appear as firm, mobile, painless slowly enlarging subcutaneous nodules which may join together to form a single mass or multilobated masses. They are covered by reddish-brown thickened skin.

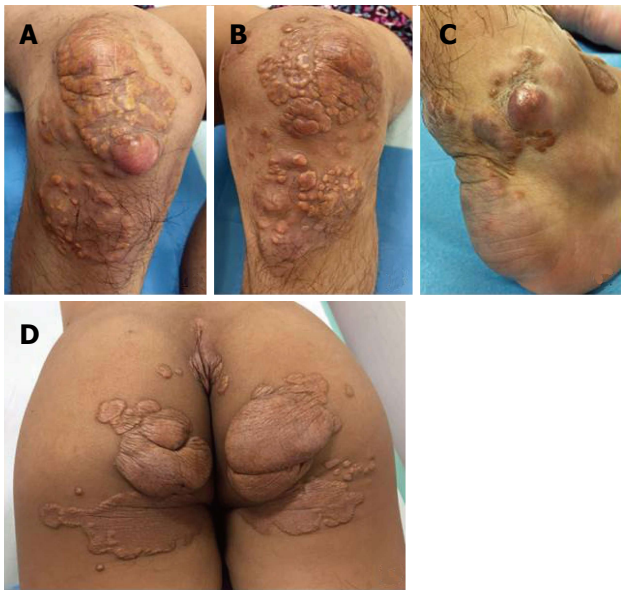


**Figure 5 Tuberous xanthomas.** They are very common and clinically variable. They may appear as firm, painless, red-yellow, waxy-appearing nodules located in the dermis and subcutaneous tissue, from few millimeters to several centimeters in size. They often present with a cobblestone-like pattern developing around the pressure areas such as: A and B: The knees; C: Malleolus; D: Buttocks. Lesions can join together to form multilobated masses.

anti-PCSK9 monoclonal antibody therapy.

## DISCUSSION

Familial hypercholesterolemia (FH), is a primary hyperlipoproteinemia characterized by an autosomal codominant genetic disorder due to mutations in the LDL receptor gene located on chromosome 19. There are two types of FH: A Homozygous FH (HoFH), in that the individuals with two mutant LDL receptor alleles are much more affected than those with one mutant allele, Heterozygous FH (HeFH)[2,6,12]. HoFH is a rare form of inherited dyslipidemia often diagnosed early in childhood which in most cases is not detected. Originally, the

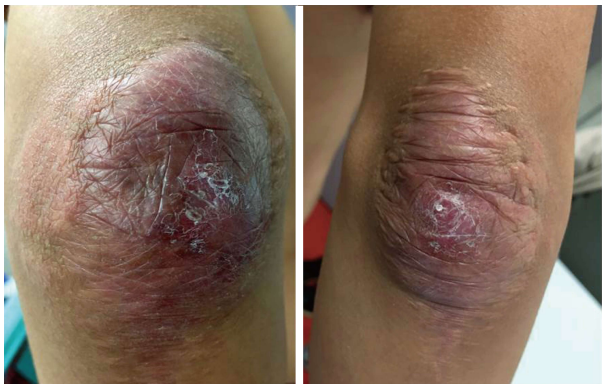

**Figure 6 Bilateral massive tuberous xanthomas of the elbows did not recur after surgical excision.**

prevalence of HoFH was estimated as 1 per million, with higher prevalence in countries with founder mutations, especially if consanguineous marriages were present. However, the HoFH prevalence is now estimated at one in 160000 to 300000[2,13]. The heteroxygous form is the most common with an incidence of 1 out 500, in which the patient has usually diagnosed as adult[12,13]. Despite published data, there is not agreement about how and when perform the screening in childhood but familial history of hypercholesterolemia in parents is crucial for detection and diagnosis of HoFH[2,11,14-16]. FH is a disease characterized by a triad: Elevated LDL-C, tendon xanthomas, and premature coronary heart disease[6]. HoFH should be suspected if both parents have HeFH where the probability of a child having HoFH is 1 in 4[16]. In HoFH patients, markedly elevated LDL-C concentration may be present at birth, as well as cutaneous xanthomas but generally present by the age of four. Corneal arcus is common by age ten and tendon xanthomas develop inevitably while coronary artery disease (CAD) develops from childhood on with high risk for a fatal or non-fatal coronary event by age thirty[5,13,15]. However, the presence of xanthomas increases the risk of CAD in patients with FH by as much as three fold. For a patient with cutaneous or tendon xanthomas, the probability of FH is very high; however, an absence of xanthoma does not rule out FH[6,15]. Epidemiologic data on cutaneous xanthomas are limited. Xanthomas are rarely seen before age twenty although those associated with FH are an exception. They tend to occur in both males and females without any sex predilection, develop inevitably and an exaggerated phenotype may be observed in patients with HoFH as was in our case[1,4,9,17,18]. The patient in the present study presented with multiple large xanthomas with a wide ranging distribution all over the body, and an onset at the age of two. The patient had an LDL-C level of 557 mg/dL, suggesting a high likelihood of HoFH. The patient was the offspring of two parents with HeFH, and appeared to have an inherited HoFH phenotype associated with an increased level of TC and serum LDL-C and more severe symptoms than the parents. The parents had mildly elevated levels of TC

(father 330 mg/mL; mother 300 mg/mL), which, when combined with the absence of xanthomas, suggests that the parents suffered from HeFH. Only a minority of patients with lipoprotein disorders have xanthomas thus the estimation of plasma lipid levels alone may not be enough to properly identify a specific lipid metabolic disorder, on the contrary the presence of xanthoma lesions represent a useful marker for these diseases[4]. Therefore it seems logical that skin lesions have been described as the first symptom. Cutaneous xanthomas were first introduced in the medical field by Rayer[19] in 1835, when he described "yellow lesions on the eyelids"[19,20]. In 1851, Addison and Gull observed various forms of xanthomas naming those "vitiligoidea"[20,21]. This term was soon replaced by xanthoma by W. Frank Smith in 1869 and descriptive terms were added, such as "planum", "multiplex" and "tuberosum"[10,12,22]. The unique association of FH and tendon xanthomas was reported by Fagge in 1873[6,23]. Xanthomas are seen in 40%-50% patients of FH and HeFH is the most common cause. Of the affected individuals 50% to 75% may complain of tendon xanthomas that rarely have been reported in the setting of normal plasma levels of cholesterol. The prevalence increases from 7% in the third decennium to 50% in the sixth decennium[1,4,10,15]. They are not palpable in up to 20% of individuals. Thus, to identify these xanthomas sonography is the most appropriate technique and is superior to clinical assessment, and even if not present an abnormal texture and thickening of Achilles tendon were demonstrated in 68% of subjects with FH[1,24,25]. Xanthelasma are seen in 23% of cases but they are the least specific of all xanthomas representing the vast majority of cases (> 95%) and because they are seen in many hyperlipidaemic and normolipidaemic states. About 65% of adult patients with xanthelasma may show normal plasma lipid levels. Tuberous xanthomas are reported in 10%-15% of cases and intertriginous xanthomas occurring occasionally[1,10]. The presence of tuberous and intertriginous xanthomas in a child with a markedly elevated plasma cholesterol level is strongly suggestive of HoFH. Intertriginous xanthomas have not been seen in the HeFH, in which plasma LDL-C are less markedly increased. In contrast, tuberoeruptive xanthomas are associated with several forms of hyperlipoproteinemia and rarely occur in patients with FH[1,4,9,10,12,16]. From detailed literature review and according to European Atherosclerosis Association Guidelines[6,13,16,26] our patient has met clinical criteria for a definite diagnosis of HoFH, even in the absence of a mutation on genetic testing, and was based on the following data: (1) High serum TC and LDL-C levels with normal triglyceride levels; (2) Appearance of xanthomas in the first decade of life; (3) Documentation of mildly elevated levels of LDL-C and TC and absence of xanthomas in both parents and in one of the siblings; (4) The presence of signs of atherosclerosis; and (5) The presence of multiple large xanthomas with a wide ranging distribution and above all, the rare pathognomonic intertriginous xanthomas, which have been described as a dermatological marker of this homozygous type.

In conclusion, this case highlights the importance of proper identification of nodular lesions and a differential diagnosis of specific subtypes of xanthomas by physicians and especially dermatologists. Xanthomas cannot be considered as simple cosmetic lesions as they are the earliest clinical indicators of lipidemic disorders. The publication of individual cases seems beneficial since this case study of HoFH wants to emphasise that this disorder remains critically under-diagnosed, and a delayed diagnosis could have potentially devastating consequences because these patients progress rapidly to atherosclerotic changes leading to aortic stenosis and CAD. Nonetheless a very important problem in these patients is that most of them do not feel ill enough until a severe CAD takes place.

## ARTICLE HIGHLIGHTS

### *Case characteristics*

Cutaneous xanthomas may or may not be present with lipid metabolic disorders, usually depending on the severity of the lipid abnormality.

### *Clinical diagnosis*

Polymorphous cutaneous xanthomas in Homozygous Familial Hypercholesterolemia (HoFH).

### *Differential diagnosis*

The presence of specific lesions represents a useful marker to properly identify a specific hyperlipidaemic disorder.

### *Laboratory diagnosis*

High serum total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels with normal triglyceride levels.

### *Pathological diagnosis*

Presence in the dermis of cholesterol crystalline aggregates surrounded by fibrosis and foamy cells.

### *Experiences and lessons*

HoFH is a rare form of inherited dyslipidemia now estimated with a prevalence of one in 160000 to 300000.

### *Treatment*

Atorvastatin, ezetimibe, low dose aspirin and LDL-C apheresis.

### *Related report*

The presence, the clinical and dermatological features of multiple large xanthomas with a wide ranging distribution and above all, the rare pathognomonic intertriginous xanthomas, have been described as a dermatological marker of the HoFH.

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