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Anthony Kodzo-Grey Venyo*

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Research Article

Verruciform Xanthoma of The Penis: Review and Update

Anthony Kodzo-Grey Venyo

Retired Urologists, Medical Examiner Member Durham, United Kingdom

***Corresponding Author:** Anthony Kodzo-Grey, Retired Urologists, Medical Examiner Member Durham, United Kingdom.

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Abstract:

Verruciform xanthoma is stated to be an uncommon, benign condition, which predominantly afflicts the oral cavity, but also the skin and female anogenital mucosa. It could be flat, papular-warty or crateriform-cystic. It could simulate HPV viral lesion such as condyloma and malignant neoplasms such as verrucous squamous cell carcinoma. An accurate diagnosis of VHP is important to avoid overtreatment, considering that it is a benign lesion which does not require any radical treatment.

Verruciform xanthoma (VX) is known to be a benign and non-destructive mucocutaneous tumour of the oral cavity. VX lesions had been noted to have manifested as flat or slightly raised lesions, which could be pink in colour, yellow in colour, or grey in colour, depending upon the degree of keratinization associated with the VX. It has been known that extra-oral involvement of VX is rare and penile VX is uncommon VX is known to simulate the presenting features of some malignant conditions, in view of this the correct diagnosis of VX is pivotal in order to avoid the undertaking of aggressive treatment procedures. Some of the differential diagnoses may of VX of the penis include: seborrhoeic keratosis (SK), verruca vulgaris, condyloma acuminatum, giant molluscum contagiosum (GMC), condyloma latum, xanthomas and squamous cell carcinoma (SCC). The gold standard means of establishing the diagnosis of Verruciform xanthoma of the penis based upon clinical examination, dermoscopy, histopathology examination of specimens of VXP lesions as well as immunohistochemistry staining studies of the penile lesions. It is important for clinicians all over the world to be familiar with the manifestations of verruciform xanthoma of the penis.

Keywords: verruciform xanthoma; penis; rare; oral cavity; clinical examination; biopsy; histopathology; immunohistochemistry; benign; differential diagnoses

Introduction

Xanthomas are lesions that are typified by accumulations of lipid-laden macrophages. [1] Xanthomas could develop in the setting of altered systemic lipid metabolism or as an emanation of local cell dysfunction. [1] Lipids are insoluble in water and hence they tend to be transported as complexes of lipoproteins and specific apoproteins. [1] These proteins also serve as ligands for specific receptors, and they facilitate transmembrane transport, as well as they regulate enzymatic activity. [1] Lipoproteins tend to be classified according to their density, as follows: chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). The metabolic pathways of lipoproteins tend to be divided into exogenous and endogenous pathways. The exogenous lipoprotein pathway entails the metabolism of intestinal lipoproteins, the triglyceride-rich chylomicrons, primarily which is formed in response to dietary fat. [1] The endogenous lipoprotein pathway entails lipoproteins and apoproteins which are synthesized within tissues other than the intestines, predominantly within the liver. [1] The liver secretes the triglyceride-rich VLDL which contains apoproteins B-100, C-II, and E into the circulation. [1]

Within the peripheral tissues, particularly adipose and muscle tissue, VLDL is cleaved by lipoprotein lipase (LPL), extracting majority of the triglycerides and forming an IDL which contains apoproteins B-100 and E. IDL can be taken up by the liver via the LDL receptor, or it could be converted to the cholesterol-rich LDL which contains apoprotein B-100. LDL is removed from the circulation primarily by the liver through the LDL receptor. [1] HDL particles which contain apoproteins A-I and A-II interact with other lipoproteins, particularly VLDL and LDL, via lipolysis and the action of lecithin cholesterol acyltransferase (LCAT) enzyme. [1] The main role of HDL is to accept cholesterol and to transport it back to the liver by reverse cholesterol transport. [1]

Lipoprotein (a) (Lp[a]) consists of an LDL-like particle with apoprotein B and a side chain of a highly glycosylated protein. Lp(a) has a role not only in atherogenesis but also in thrombogenesis due to its homology with plasminogen. [1]

Alterations in lipoproteins emanate either from genetic mutations which yield defective apolipoproteins (primary hyperlipoproteinemia) or from some other underlying systemic disorder, such as diabetes mellitus, hypothyroidism, or nephrotic syndrome (with secondary hyperlipoproteinemia). [1] The biochemical and genetic basis for the

inherited disorders of lipid and lipoprotein metabolism do differ considerably. [1]

Traditionally, hyperlipidemias had been classified according to 6 phenotypes which had been described by Fredrickson. These phenotypes are based upon the electrophoretic patterns of lipoprotein level elevations which occur in patients with hyperlipoproteinemia. [1] Over recent years, the understanding of the genetic and biochemical basis of these disorders had demonstrated a large and diverse group of diseases, many of which do have similar clinical expressions, exposing the limitations of the Fredrickson classification system. It has been iterated that despite the system's shortcomings, Fredrickson phenotypes are a useful tool for the discussion of these disorders. [1] It has been pointed out that the comprehension of the pathophysiology of these defects provides a basis for diagnosis and treatment. [1]

It has been explained that familial lipoprotein lipase deficiency is an example of a primary disorder in which a deficiency of lipoprotein lipase in tissue does lead to a type I pattern of hyperlipidemia, with a massive accumulation of chylomicrons in the plasma. [1] This effect is stated to emanate in a severe elevation of plasma triglyceride levels. [1] It has been iterated that plasma cholesterol levels are not usually raised. [1] It has been stated that patients with type I may manifest in early childhood, often with acute pancreatitis.[1] It has been pointed out that eruptive xanthomas are the most characteristic skin presentation of this disorder. [1] It has been iterated that a case that was reported in 2020 described this type of xanthoma as the manifesting and only sign of undiagnosed diabetes mellitus. [1] [2] The cutaneous lesions resolved within 3 months of diet modification and correction of lipid and glycemic parameters. [1] [2]

Cholesterol is bound to apolipoprotein B-100 as LDL in interstitial fluid. Cells could acquire cholesterol through an LDL receptor upon the cell membrane. [1] Familial LDL receptor deficiency and familial defective apoprotein B-100 are stated to be examples of primary defects that could lead to the accumulation of LDL, that corresponds to a type IIa pattern of hyperlipidemia. [1] Plasma cholesterol levels are severely raised, but plasma triglyceride levels are typically normal. Patients with type IIa do have severe atherosclerosis. [1]

The type IIb pattern is stated to be typified by the accumulation of both LDL and VLDL, with variable elevations of both triglyceride levels and cholesterol levels in the plasma. [1] it has been pointed out that patients with familial combined hyperlipoproteinemia have such a pattern of hyperlipidemia, but a specific genetic defect has not been established. [1]

It has been iterated that patient who have type IIa and IIb may manifests as adults with tendinous and tuberous xanthomas and xanthelasmas. [1]

It has been pointed out that type III hyperlipidemia is typified by the accumulation of IDL (beta-VLDL), which is presented by increases in both triglyceride levels and cholesterol levels in the plasma. [1] A genetic basis for the primary disorder, familial dysbetalipoproteinemia, had been well established. [1] It has been iterated those various mutations of apoprotein E impair its ability to bind to the IDL receptor. [1] Patients with type III manifest as adults with premature atherosclerosis and, particularly, plane (palmar) xanthomas. [1] [3] It has been explained that familial hypertriglyceridemia is an example of a primary defect emanating in type IV hyperlipidemia. [1] Accumulation of VLDL does cause severe rises of plasma triglyceride levels. [1] Plasma cholesterol levels are typically normal. [1] A definitive molecular defect had not been established. [1] It has been stated that patients with type IV may manifest with eruptive xanthomas. [1]

It has been pointed out that genetic defects of the apolipoprotein C-II gene emanate in the accumulation of chylomicrons and VLDL, which is the type V pattern of hyperlipidemia. [1] It has been stated that patients with this type have severe elevations of triglyceride levels in the plasma. [1] These patients, like those with lipoprotein lipase deficiency, may manifest in early childhood with acute pancreatitis and eruptive xanthomas. [1] [4] It has been pointed out that decreased synthesis of HDL due to decreased formation of apoprotein A-I and apoprotein C-III does lead to decreased reversed cholesterol transport, resulting in increased LDL levels, premature coronary artery disease, and plane xanthomas. [1]

It has been iterated that normolipemic xanthoma might occur as xanthoma disseminatum, diffuse-plane normolipemic xanthomatosis, and verruciform xanthoma. [1] In these patients with normal lipid profiles, inflammation and trauma/local tissue injury are considered or understood to be the implicating factors in the development of the cutaneous lesions. [1] These patients are stated to be at risk for underlying myeloproliferative disorders and should be evaluated for paraproteinemia. [1]

Xanthoma disseminatum is a non–Langerhans cell of class II histiocytic disorder. [1] [5] It has been stated that the aetiology is unknown; however, it is usually associated with diabetes insipidus. [1] [6] It had also been stated that familial inheritance is not certain. [1] [7]

Diffuse-plane xanthomatosis is a rare, noninherited disorder related to diseases of the reticuloendothelial system. [1] [8] The pathogenesis had remained not clear but it is often associated with multiple myeloma and monoclonal gammopathy. [1] In 2020, diffuse normolipidemic–plane xanthoma was reportedly seen in association with necrobiotic xanthogranuloma. [9] Verruciform xanthoma is considered to be a reaction pattern to chronic inflammation or trauma or a result of impaired lymphatic function. [1] [110] [11] [12] A case of verruciform xanthoma which had appeared 3 years pursuant to resection of genital Paget disease was reported in 2021. [13] It has been iterated that cerebrotendinous xanthomatosis is an uncommon serious autosomal recessive disorder of bile acid synthesis. It is categorized as an adult lipid storage disorder with known mutation in the *CYP27A1* gene; there is resultant deficiency in sterol 27-hydroxylase. [1] Cholesterol and cholestanol deposits then accumulate within the nervous system and tendons; hence, neurologic clinical and diagnostic imaging findings and tendon xanthomas are the characteristic findings. [1] [14] Hyperlipidemia is also related to a variety of secondary causes. Secondary hypercholesterolemia could be found in pregnancy, hypothyroidism, cholestasis, and acute intermittent porphyria. Secondary hypertriglyceridemia could be associated with diabetes mellitus, alcoholism, pancreatitis, gout, sepsis due to gram-negative bacterial organisms, and type I glycogen storage disease. [1] Combined hypercholesterolemia and hypertriglyceridemia could be found in nephrotic syndrome, chronic renal failure, and steroid immunosuppressive therapy. [1] [15] [16] Iatrogenic causes of hypertriglyceridemia must also be screened. Drug-induced hypertriglyceridemia should be taken into consideration in patients taking long-term isotretinoin, sodium valproate, protease inhibitors, sertraline, thiazide diuretics, oral contraceptive pills, cyclosporine, or tacrolimus. [1] [17] Xanthomas are a common manifestation of lipid metabolism disorders. Xanthelasmas comprise 6% of eyelid tumours. [1] [18] Equal prevalence of xanthoma has been reported in males and females. [1] Xanthoma disseminatum occurs in a male-to-female ratio of 2.4:1.[1] [19] It has been stated that xanthomas may occur in persons of any age. Xanthelasmas usually occur in people older than 50 years. It has been stated that xanthoma disseminatum occurs before age 25 years in two thirds of cases. [1] [19] It has been stated that cutaneous xanthomas are mostly cosmetic disorders; their presence might suggest an underlying disorder of lipid metabolism.[1] It has also been stated that recurrences post-surgical treatment of xanthomas are common. It has been iterated that significant mortality and morbidity arise in patients with involvement of functional anatomic sites in xanthoma disseminatum. [1] [20] Otherwise, it has been stated that the course of the disease is benign. [1] Nevertheless, the common types persist and the rest either resolve spontaneously or progress. [1] [6] [21]. It has been iterated that morbidity and mortality are related to atherosclerosis (eg, coronary artery disease) and pancreatitis. Considering that Verruciform xanthoma of the penis is not common, it would be envisaged that majority of clinicians all over the world would not have encountered a case before and they may therefore not be familiar with the manifestations, treatment and outcome of verruciform xanthoma of the penis. The ensuing article on verruciform xanthoma of the penis is divided into two parts: (A) Overview and (B) Miscellaneous narrations and discussions from some case reports, case series, and studies related to verruciform xanthoma of the penis.

Aim

- To review and update the literature on verruciform xanthoma of the penis.

Method

Internet databases were searched including: Google; Google scholar; Yahoo; and PUBMED. The search words that were used included: Verruciform xanthoma of the penis; and penile verruciform xanthoma. Eighty-one (81) references were identified which were used to write the article which has been divided into two parts: (A) Overview which has discussed general aspects of verruciform xanthoma, and (B) Miscellaneous narrations and discussions from some case reports, case series, and studies related to verruciform xanthoma of the human penis.

Results

[A] Overview

Definition / general statement

- Verruciform xanthoma is an uncommon, nonneoplastic lesion of verrucous epidermal acanthosis, foamy histiocytes aggregates in papillary dermis and neutrophilic inflammation. [22]

Essential features

- Verruciform xanthoma is a non-neoplastic verrucous lesion which is characterized by aggregates of lipid laden macrophages in papillary dermis. [22]
- Verruciform xanthoma closely simulates other verrucous lesions clinically and microscopically. [22]

Epidemiology

The epidemiology of verruciform xanthoma had been summated as follows: [22]

- Mean age: 54.5 years to 62 years; age range: 8 years to 85 years. [23] [24]
- M > F Verruciform xanthoma affects males more commonly in comparison with females. [24]
- Majority of cases of verruciform xanthoma had been reported in Caucasians. [23]
- It has been iterated that verruciform xanthoma may be present several years before its diagnosis is established. [23]

Sites

The sites of the human body affected by verruciform xanthoma has been summated as follows: [22]

- Verruciform xanthoma is stated to be usually found in the oral cavity and majority of non-oral cases of verruciform xanthoma involve the anogenital skin including the penis, scrotum and vulva). [23] [25]

Aetiology

- It has been iterated that the aetiology of verruciform xanthoma is not certain, and that the aetiology is likely local irritation, inflammation or trauma inciting an immune reaction with consequent keratinocyte degradation. [10] [26] [27]
- The aetiology of verruciform xanthoma does entail keratinocyte degradation resulting in release of chemotactic cytokines, attracting neutrophils as well as plasma cells and lymphocytes. [22]
- The aetiology of verruciform xanthoma does involve macrophages **(CD68+ dermal dendritic cells)** phagocytose neutrophilic and keratinocyte debris with eventual formation of foamy cells. [22], [26] [28]
- HPV association in verruciform xanthoma is stated to be variable. [10] [25]
- Verruciform xanthoma has been documented in several reports coexisting with inflammatory cutaneous disorders (graft versus host disease, pemphigus vulgaris, discoid lupus erythematosus, lichen planus) or associated with immunocompromise. [22]
- Not associated with underlying disorders of lipid metabolism. [10]

Clinical features

The clinical features of verruciform xanthoma had been summated as follows: [22]

- With regard to manifestation, verruciform xanthoma has tended to be asymptomatic, slow growing, persistent and usually solitary papule(s) or plaque resembling viral warts, particularly on the scrotum in males. [23] [24
- Difficult to distinguish clinically; may resemble fibroepithelial polyp, seborrheic keratosis, condyloma acuminatum, squamous cell carcinoma or verrucous carcinoma. [24]

Diagnosis

- It has been iterated that diagnosis of verruciform xanthoma is established based upon punch biopsy of the lesion with subsequent histological examination of the biopsy specimen. [22]

Treatment

- With regard to treatment, it has been iterated that majority of cases of verruciform xanthoma are cured by complete excision and that typically the lesions do not recur. [22] [23]

Gross description

- It has been iterated that macroscopy pathology examination of specimens of verruciform xanthoma of human beings demonstrates yellow, pink, brown, or flesh-coloured pedunculated papules or plaques, that measure between 0.5 cm and 2.5 cm, with a verrucous or pebbly surface. [22] [23] [24] [25]

Microscopic (histologic) description

It has been iterated that microscopy pathology examination of specimens of verruciform xanthoma does demonstrate the ensuing features: [22]

- Verrucous epidermal acanthosis, papillomatosis and hyperkeratosis. [22]
- Uniform depth of rete ridges. [22]
- Parakeratosis, which often has tended to be wedge shaped, filling clefts between epidermal projections. [22] [24]
- Large foamy histiocytes (lipid laden macrophages) in aggregates in elongated dermal papillae, may be scattered or scarce. [22] [23] [24] [27]
- Neutrophils, particularly within the stratum corneum, as well as in the dermis and occasionally prominent neutrophilic exocytosis. [22] [23] [24] [25
- Mixed inflammatory infiltrate within the submucosa [22] [27]
- Vascularized papillary dermis. [22] [29]

- Absence of keratinocyte atypia. [22]

Immunohistochemistry staining studies

The immunohistochemistry staining studies features of verruciform xanthoma had been summated as follows: [22]

Positive stains

The positive immunohistochemistry staining features of verruciform xanthoma specimens had been summated as follows: [22]

- Foamy cells: **CD68+**, **PAS+** and **diastase** resistant. [30] [31]
- **Adipophilin.** [32]
- **Factor V111a.** [22]
- **Vimentin.** [22]

Negative stains

The negative immunohistochemistry staining features of verruciform xanthoma specimens had been summated as follows: [22]

- **S100.** [33]

Electron microscopy description

- Xanthoma cells upon electron microscopy studies are found to contain membrane bound lysosomes, myelin figures and fragmented desmosomes. [22] [34]
- Verruciform xanthoma

Differential diagnoses. [22]

The differential diagnoses of verruciform xanthoma had been summated to include the following: [22]

- **Verruca vulgaris**:
  - Koilocytes, coarse hyper-granulosis, prominent papillomatosis, rete ridges curve inward
- **Condyloma acuminatum**:
  - Prominent koilocytotic atypia within the upper epidermis.
  - No prominent foamy macrophages.
- **Xanthoma**:
  - Foamy cells are located in the mid dermis.
  - Clinical hyperlipidemia.
- **Squamous cell carcinoma**:
  - Marked atypia, no prominent foamy histiocytes.
- **Verrucous carcinoma**:
  - Ulcerating or fungating lobules of mature squamous epithelium.
  - Minimal atypia but no prominent foamy histiocytes.
- **Bowenoid papulosis**:
  - Mimicking basaloid **PeiN.**
  - Spotty cytological atypia.

[B] Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Studies Related to Verrucous Xanthoma of The Penis

Sette et al. [35] reported a-16-year-old boy, who had manifested with difficulty in exposing his glans penis. He had undergone postectomy 6 years earlier. His clinical examination demonstrated obstructive phimosis, and a new corrective procedure was indicated. During the undertaking of his surgery, erythematous yellowish confluent papules, that measured between 10 mm 20 mm in size, were observed upon his penis, and these had formed a verrucous and well-defined plaque, partially compromising the glans penis. The lesions were confirmed upon pathology examination to be verruciform xanthoma of the penis. A lesson learnt from this short case summation is the fact that even though rare, verruciform xanthoma of the penis could develop a number of years pursuant to the undertaking of postectomy.

Hedge et al. [27] made the ensuing iterations:

- Verruciform xanthoma is a papillary or cauliflower-like growth, which is typically seen chiefly within the oral mucosa.
- Verruciform xanthoma was first described by Shafer in 1971. [36
- Vx is an uncommon lesion, which has been associated with an incidence rate of 0.025-0.05% of all the pathology cases and hence had been usually diagnosed clinically as papillomas.
- Nevertheless, the histopathological findings are diagnostic of these lesions.
- Very few cases of verruciform xanthoma occurring within the extra-oral regions had been reported.
- The extraoral Vx lesions had tended usually to be associated with other conditions such as lymphedema, epidermal nevi and Congenital Hemidysplasia with Ichthyosiform erythroderma and Limb Defects (CHILD) syndrome. [37]
- Even though, the presence of foamy histiocytes within the elongated dermal papillae constitutes the hallmark of histopathology examination diagnosis of verruciform xanthoma, the nature and origin of these foam/xanthoma cells had remained debatable in the past and during current times.
- Various pathogenic mechanisms for the development of Vx had been put forth to explain the presence of xanthoma cells in verruciform xanthoma.
- The latest concept in its etiopathogenesis is an immune mechanism to local trauma or inflammation. The immunohistochemical studies had demonstrated that the predominant cells in the inflammatory infiltrate are T cells.[38]
- The foam cells are considered to be of monocyte/macrophage lineage, since they are positive to CD68 antibody (a macrophage marker).[28]

Kraemer et al. [39] reported a patient who had been afflicted by a verruciform xanthoma of his penis. They iterated that histopathology examination of specimens of VX usually demonstrate that the distinctive lesion is usually confined to the oral mucosa, even though two cases occurring upon the vulva had recently been reported. Kraemer et al. [39] also stated the ensuing:

- To their knowledge, this lesion of VX had not been described before 1981 August in other sites (extra-oral sites).
- Biopsy of the penile lesions for histopathology examination is required in order to aid in the identification of this unusual entity.
- Verruciform xanthomas had been benign in their biology behaviour, even though a squamous cell carcinoma had subsequently developed in one patient whose oral lesions were associated with leukoplakia.

Cuozzo et al. [40] stated the ensuing:

- Verruciform xanthoma is an uncommon benign lesion.

- The majority of the cases of verruciform xanthoma occur upon the oral mucosa.
- Nevertheless, other sites, particularly the anogenital region, may be involved by verruciform xanthoma.

Cuozzo et al. [40] reported the eleventh case in the literature of verruciform xanthoma of the penis. Cuozzo et al. [40] also made the ensuing iterations:

- The diagnosis of genital verruciform xanthoma is significant, due to the fact that it could simulate verrucous carcinoma or invasive squamous cell carcinoma.
- Proper diagnosis of verruciform xanthoma by clinical recognition, adequate but limited biopsy and histopathology examination of the biopsy specimen would avoid the undertaking of unnecessarily aggressive surgical procedures for the treatment of the verruciform xanthoma lesion.

Takiwaki et al. [41] reported a case of squamous cell carcinoma of the penis, which seemed to have arisen within a verruciform xanthoma of his penis. He had manifested with a lesion within his prepuce, that was initially diagnosed as a verruciform xanthoma based upon histopathology examination of specimens of the penile lesion which had been removed in part. Six years subsequently, the patient exhibited a well-differentiated squamous cell carcinoma of his penis which contained many clusters of xanthoma cells within the stroma. Even though retrospective examination of biopsy specimens of his initial penile lesion had demonstrated features that were mainly of verruciform xanthoma, significant architectural and cytological atypia was also noted to be present within the overlying epidermis. In view of their experience, Takiwaki et al. [41] advised that clinicians should take care not to overlook the presence of a squamous cell carcinoma arising within a benign reactive lesion such as a verruciform xanthoma.

De Rose, et al. [42] stated that verruciform xanthoma is a rare and benign condition predominantly afflicting the oral cavity, but also the skin as well as the female anogenital mucosa. It could be flat, papular-warty or crateriform-cystic. Furthermore, it could mimic HPV viral lesion such as condyloma and malignant neoplasia such as verrucous squamous cell carcinoma. An accurate diagnosis is important to avoid overtreatment, considering it is a benign lesion that does not require any radical treatment. They had reported an extremely rare case of a 64-year-old man with a small, slightly raised, grey reddish-dotted lesion upon the left portion of the ventral side of his glans penis.

Beutler et al. [43] iterated the following:

- Verruciform xanthoma is a benign verrucous lesion, that is typified by epithelial acanthosis and lipid-laden foamy histiocytes within the connective tissue papillae.
- Verruciform xanthoma typically manifests as a papillomatous, polypoid, or sessile lesion.
- Verruciform xanthoma is most commonly found within the oral cavity.
- Nevertheless, albeit less frequently, verruciform xanthoma does develop upon the penis, scrotum, or vulva sporadically.

Beutler et al. [43] reported the clinical and pathologic findings of a man who developed a verruciform xanthoma upon his scrotum. Beutler et al. [43] also summated the associated conditions, the differential diagnosis, the postulated pathogenesis, and the treatment options for verruciform xanthoma. Beutler et al. [43] reported the features of a man who was afflicted by a scrotal verruciform xanthoma. Utilising PubMed, the following terms were searched and relevant citations were assessed by Beutler et al. including: anogenital, foam cells, penis, scrotum, verruciform, verruciform xanthoma, vulva, and xanthoma. In addition, they reviewed the literature on verruciform xanthoma. Beutler et al. [43] summarised the results as follows:

- Their patient developed had manifested with an asymptomatic, exophytic, red filiform papule on his scrotum.
- A shave biopsy, attempting to remove the entire lesion, was undertaken.
- Based upon correlation of the clinical manifestation and histopathology examination findings of specimens of the biopsied lesions, a diagnosis of verruciform xanthoma was made.
- The patient applied mupirocin 2% ointment to the biopsy site, which subsequently healed without complication or recurrence.

Beutler et al. [43] made the ensuing conclusions and discussions:

- Verruciform xanthoma is a benign tumour, which is commonly found within the oral cavity and which is typified by the development of a small verrucous, papillomatous, polypoid, or sessile growth.
- Extra-oral sites of verruciform xanthoma often include the penis, scrotum, or vulva and they had introduced the terminology 'Vegas' (Verruciform Genital-Associated) xanthoma for these lesions.
- The lesions had often been mistaken for viral warts or malignancies.
- Even though the mechanism of pathogenesis is not known, verruciform xanthoma might be associated with a multifactorial aetiology that involve inflammation, local immunosuppression, and/or metabolic dysfunction.
- It has also been promulgated that verruciform xanthoma is a secondary reaction to trauma-induced epithelial damage or degeneration.
- A biopsy for histopathology examination is necessary to diagnose verruciform xanthoma.
- The treatment of verruciform xanthoma typically entails simple surgical excision of the lesions.

In 2012, Joshi and Ovhal [44] reported five cases of verruciform xanthoma (VX). The patients, who were all males, had manifested with single warty verrucous lesions that measured between 0.5 cm and 2 cm in size which had been diagnosed clinically as viral warts in four cases and leukoplakia, in one case. Two patients had the lesion within the oral cavity, two upon the genital mucosa, and one upon the scrotal skin. Histopathology examination of specimens of the lesions was diagnostic, with verrucous and papillomatous epidermal hyperplasia with the silhouette of a viral wart but with numerous foamy histiocytes packed in the elongated dermal papillae. Columns of deep parakeratosis and neutrophils in the upper spinous layers, with a dermal plasma cell infiltrate were the other histopathology examination features of the lesions. Excision of the lesions was documented to be curative, without recurrences, in the two patients who had lesions within the oral cavity; follow-up was not available in the cases with genital lesions. Joshi and Ovhal [44] pointed out that VX is an uncommon but distinctive clinical and pathology entity which afflicts the oral and genital mucosa and which may be mistaken for benign, premalignant, and malignant conditions, as well as VX could be diagnosed with certainty only on histopathology examination of specimens of the lesions. Joshi and Ovhal [44] made the ensuing educative iterations:

- Verruciform xanthoma in Indian literature had been described within the oral cavity but not from genital skin
- Verruciform xanthoma (VX) is a rare clinicopathologic entity which primarily afflicts the oral and genital mucosa.

- Clinically, VX does tend to manifest as a sessile, papillary, granular, or verrucous lesion, which has often been mistaken for a viral wart.
- Collections of many foam cells in the elongated dermal papillae is a diagnostic feature of VX.
- It had been iterated that Shafer,[36] in 1971, had described 15 cases of VX within the oral cavity and had coined the term 'verruciform xanthoma.' Following this first report, many cases had been reported confirming VX as a distinctive clinicopathologic entity that manifests clinically as a single verrucous or warty plaque and is typified histologically by papillomatous epidermal hyperplasia with parakeratosis and the presence of neutrophils in the upper spinous layers. [36]
- It has been documented that the histopathology examination hallmark of VX lesion; nevertheless, is the presence of numerous foam cells within the elongated dermal papillae. [45] [46]
- It had been iterated that VX also does occur within non-oral sites and the first report of involvement of an extra-oral site, which had involved the vulva was reported by Santa Cruz in 1979. [47] Since then, many reports of VX in non-oral sites, especially upon anogenital skin, had appeared in the literature. [48] [49] [50] [51]
- VX has been iterated to have a slight male preponderance, with a reported male to female ratio of 1.1: 1. [52]

Joshi and Ovhal [44] in their article reported five cases of VX which is a rare clinical entity. Shi and Ovhal [44] reported the following:

- Their review of the biopsies which had been received in consultation over the preceding 12 years (1999–2010) had demonstrated five cases [see table 1 for summation of the cases] that fit in with the clinicopathological diagnosis of VX.

Description of cases

Sex	Age	Site	Duration of lesion
Male	40	Left buccal mucosa	1 year
Male	22	Right anterior margin of tongue	6–8 months
Male	45	Inner prepuce	Not available
Male	Na	Coronal sulcus	Not available
Male	Na	Scrotum	Not available

Table 1: Reproduced from [44] under the Creative Attribution License.

- All five cases of VX had afflicted males and had manifested with single, asymptomatic, verrucous/warty lesions which had gradually grown in size over many months.
- Two cases had afflicted the oral mucosa: One, VX which measured about 2.5 cm in size, had afflicted the left lower buccal mucosa at the level of the 1st and 2nd left molar teeth [see figure 1] and the other on the anterior right margin of his tongue as a raised verrucous papule. Both patients were smokers and case 1 also had history of chewing tobacco for 8 years preceding his manifestation. There was no bleeding from the lesions and no history of sensitivity to hot or spicy foods was obtained. There was no other relevant past or present medical history. The clinical diagnosis in the first case was leukoplakia, while in the second it was viral wart.

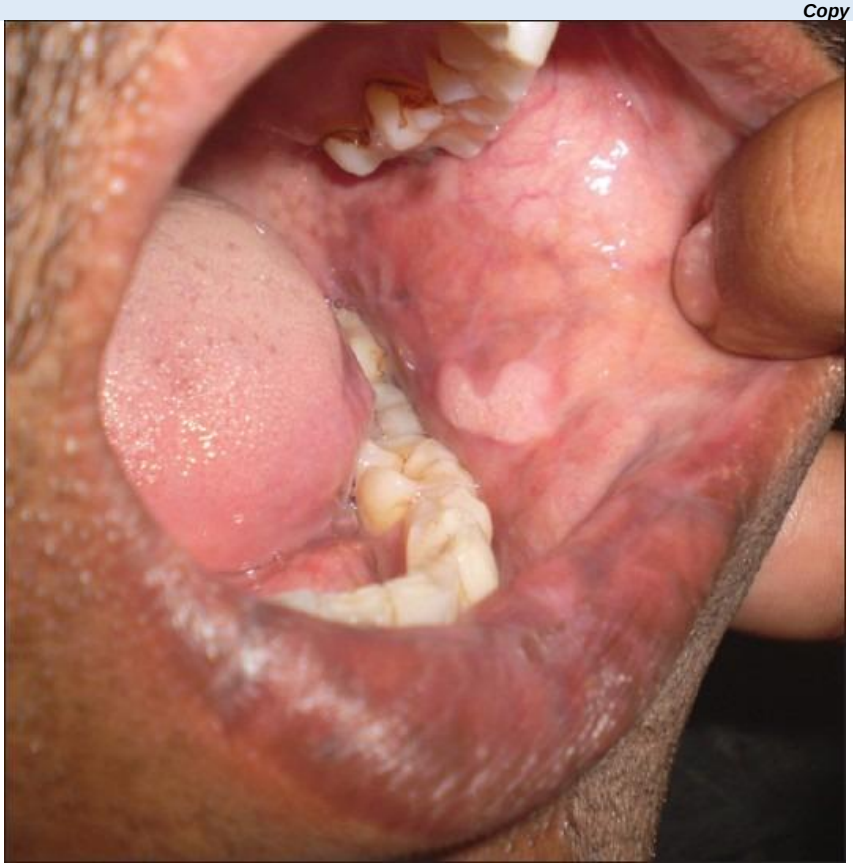

Figure 1: Verrucous plaque on the left buccal mucosa (case 1). Reproduced from [44] under the Creative Attribution License

- Cases 3 and 4 had developed single flat warty lesions upon the penile skin, upon the inner prepuce in case 3 and upon the dorsum of the penis just proximal to the coronal sulcus in case 4. Case 5 had a single lesion upon his scrotal skin. The clinical diagnosis in each of these cases was viral wart. Further clinical details and sexual history was not available for these reported patients.
- Case 1 was screened for serum lipids and all the results were found to be within their normal ranges.
- The results of the biopsy findings in all five cases were documented to be similar and had consisted of papillomatous and digitate epidermal hyperplasia, with some incurving of peripheral rete, giving the overall silhouette of a wart [see figure 2]. The upper spinous layers were noted to be infiltrated by many neutrophils which had aggregated upon the surface of the lesion [see figure 3]. The elongated dermal papillae were stuffed with foamy histiocytes with small central nuclei and abundant finely vacuolated cytoplasm [see figure 4]. Parakeratosis was not evident in all cases but was very prominent in case 2 [see figure 5], with surface and deep invaginations of columns of parakeratosis throughout the hyperplastic epidermis. The base of the exophytic epidermal lesions were noted to have contained moderately dense infiltrates of plasma cells.

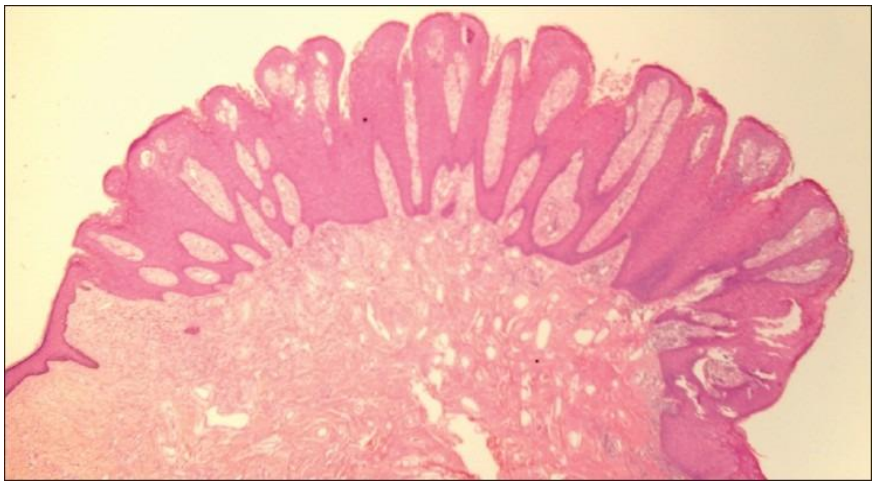

Figure 2: Exophytic papillomatous epidermal hyperplasia with silhouette of wart (H and E; 20×) (case 3). Reproduced from [44] under the Creative Attribution License.

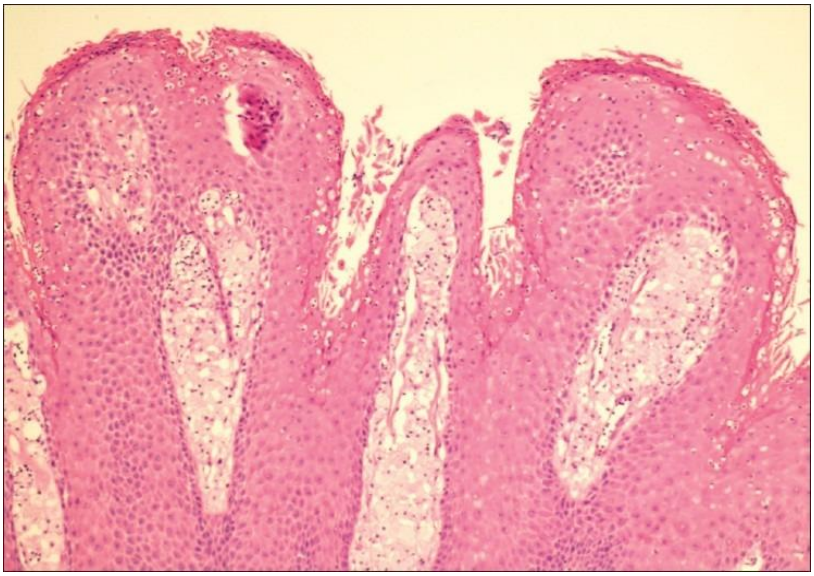

Figure 3: Neutrophils in the upper spinous layers, with foamy histiocytes in the dermal papillae (H and E; 100×) (case 3). Reproduced from [44] under the Creative Attribution License

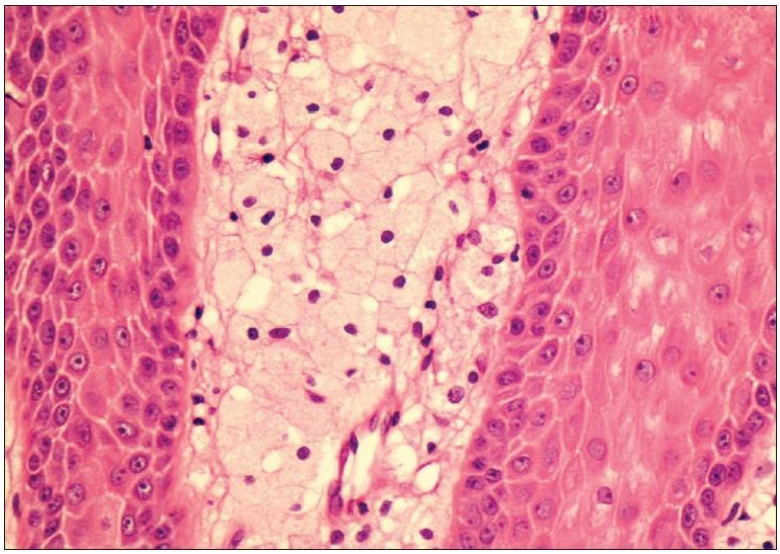

Figure 4: Elongated dermal papillae stuffed with foam cells (H and E; 400×) (case 3). Reproduced from [44] under the Creative Attribution License**.**

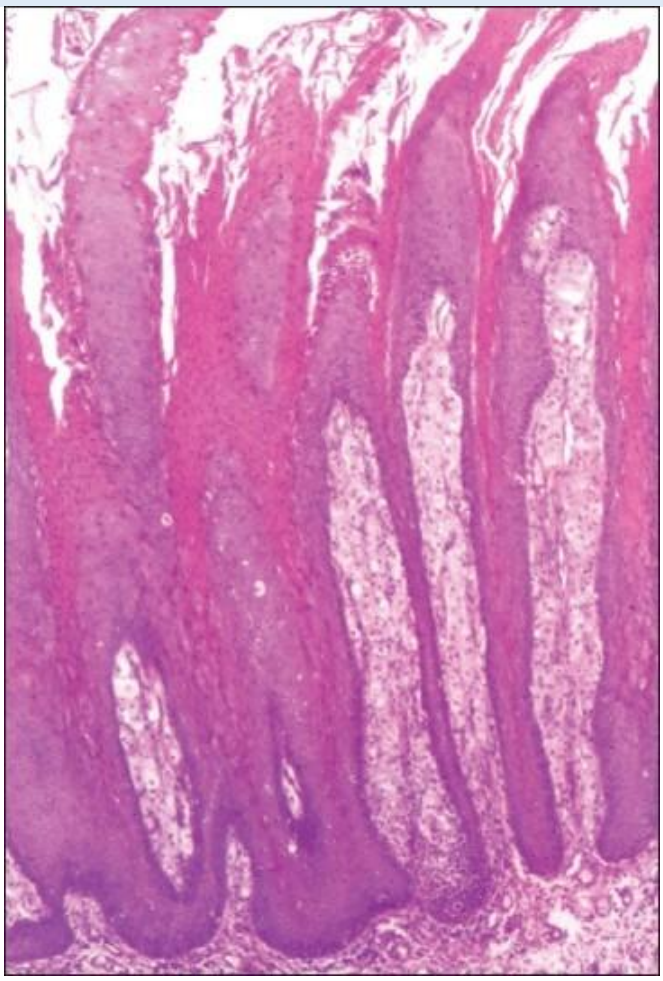

Figure 5: Deep invaginated columns of parakeratosis (H and E; 40×) (case 2). Reproduced from [44] under the Creative Attribution License.

- Features of human papilloma virus (HPV) infection, namely hypergranulosis and koilocytosis, were not visualised within any of the biopsies.
- The lesions were excised, with no recurrence, in cases 1 and 2; the others cases had been lost to follow-up assessment.

Joshi and Ovhal [44] made the ensuing educative discussions:

- VX, is a rare clinical entity and they could find only two publications on the subject in the Indian literature which had consisted of a total of three cases, all in the oral cavity). [53] [54]
- The three cases of genital VX that they had report were, to the best of their knowledge, the first report of non-oral VX that had been reported from India. This might be related to lack of awareness of this condition or possibly reluctance to biopsy warty lesions of the genital mucosa and instead to treat them as viral warts/condylomata, which is the usual clinical diagnosis.
- Upon the basis histopathology and morphological appearance, the epithelial changes of VX had been divided into three groups including: [52]–verrucous, papillary, and flat—and these epithelial changes reflect the clinical picture of the lesion.
- The diagnostic histopathology examination finding of all VX; nevertheless, whether intra- or extra-oral in location, is the presence of foam cells which fill the dermal papillae and submucosal space. These foam cells had been demonstrated to have monocyte/macrophage lineage. [52]
- Two aspects of VX had remain not resolved, namely the aetiology and the pathogenesis of lipid-laden macrophages within the dermal papillae and submucosa.
- Due to the clinical appearance and histological silhouette that closely simulates HPV-induced lesions like verrucae and condylomata and because the common sites of occurrence of VX is the oral and anogenital skin and mucosa (sites common for HPV infection), HPV infection had always been a strong contender as the etiologic agent for this condition. Many authors had not found any evidence for the presence of HPV in these lesions. [55] [56] [57] Nevertheless, contrary findings of multiple HPV DNA in VX had also been documented. [58]
- With regard to the pathogenesis of lipid-laden macrophages within the dermal papillae, Zegarelli et al., [59] had postulated that initial damage to keratinocytes by an inciting agent is ensued by degeneration of keratinocytes, which attracts dermal dendrocytes to engulf the debris and these develop into foam cells as a result of ingestion of lipids from the degenerating keratinocytes in the subepithelial dermis.
- The probable pathogenesis of VX had been suggested to be as follows: [55] 'Pursuant to keratinocyte damage by an as yet unknown inciting agent, cytokines chemotactic for neutrophils are released, with rapid growth of the epidermis that leads to the verruciform architecture and parakeratosis. The damaged and degenerating keratinocytes that move downwards into the papillary dermis and submucosal region are then engulfed by

dendritic cells, that develop into foam cells, losing in the process their normal histiocytic markers and stain negative for factor XIIIa.'

- Xanthomatous changes within the papillary dermis, that are similar to that in VX, had been reported in association with many diseases, including mycosis fungoides, [60] epithelial nevi, [61] [62] and dystrophic epidermolysis bullosa. [63] [64] The changes might histologically simulate true VX and are regarded to be a form of dystrophic xanthomatosis which possibly arises due to repeated epidermal or dermal damage, with accumulation of lipids within macrophages.

- Simple excision of the lesion did appear to be curative treatment; nevertheless, a 30-year-old woman, who had a recurrent VX of the vulva 8 years pursuant to her initial treatment has been reported in literature. [65]

Joshi and Ovhal [44] made the ensuing conclusions:

- VX could be confused clinically with benign, premalignant, and malignant lesions like viral genital warts (condylomata acuminata), leukoplakia, and verrucous carcinoma, and may even be associated with squamous cell carcinoma. [66]

- Genital warts that had been induced by HPV are almost always multiple and therefore a single asymptomatic verrucous lesion upon the oral or genital mucosa should always be subjected to biopsy in order to confirm the diagnosis and exclude malignancy. A definite diagnosis of VX can only be made on histopathologic examination.

- Their reported case series was, to the best of their knowledge, the first report of extraoral lesions of VX from India.

- They had reported these cases so as to increase the awareness regarding this rather uncommon but distinctive condition which should be taken into consideration in the differential diagnoses of solitary verrucous lesion on mucosal sites, both oral and genital.

- Nonoral (genital skin) verruciform xanthoma had been reported for the first time in Indian cases.

Kobaner et al. [67] made the ensuing iterations:

- Verruciform xanthoma is an uncommon benign lesion of unknown aetiology.

- Even though verruciform xanthoma primarily afflicts the oral mucosa, the genital area including vulva, scrotum and penis might also be involved.

- By 2018, only 33 cases of penile form had been reported in the literature. [23] [35] [42] [68] [69]

Kobaner et al. [67] reported a man, who had a 2-month history of a rapidly growing asymptomatic exophytic tumoral lesion upon the ventral part of his penis. The lesion had measured 1 cm × 1 cm and had shown a combined morphology with a yellowish, erythematous, verrucous base and a bright yellowish-pink, pedunculated component with a papillomatous, "mulberry-like" surface. He had undergone a traditional circumcision procedure during his childhood. The results of his blood tests were within the normal levels and his serology for hepatitis and human immunodeficiency virus was negative.

An incisional biopsy which had involved the papillomatous part of the tumour had shown verruciform acanthosis within the epidermis and numerous lipid-laden, foamy histiocytes in the papillary dermis, demonstrating a diagnosis of verruciform xanthoma. In additional, p16 immunohistochemistry staining studies results demonstrated only a weak patchy staining of epidermal cells, which had excluded a possible human papilloma virus infection in the pathogenesis. Complete surgical excision was planned, but the patient refused to undergo surgical treatment. During his 20-month follow-up assessments, no change was noted within the remaining basal portion of the tumour. Kobaner et al. [67] made the ensuing educative discussions:

- The etiopathology of verruciform xanthoma had remained to be elusive up to the time of publication of their case.

- An association with human papillomavirus infection or lipid disorders had been suggested, but this had not been confirmed, in most of the patients. [68].

- Due to its association with lichen planus, an autoimmune etiopathology including apoptosis of epithelial cells had also been postulated [23] The latest concept; nevertheless, has been based upon a traumatic or inflammatory injury emanating in keratinocyte degeneration and an inflammatory reaction, which induces macrophages to engulf lipid material released from the epithelial cells and become lipid-laden, foamy histiocytes. [42]

- The xanthomatous appearance in verruciform xanthoma is stated to be related to the presence of these subepithelial foamy histiocytes and epithelial hyperplasia is a secondary change.

- Verruciform xanthoma might occur within the setting of a variety of cutaneous disorders such as congenital hemi-dysplasia with ichthyosiform erythroderma and limb defects (CHILD syndrome), inflammatory linear verrucous epidermal nevus and dystrophic epidermolysis bullosa, which is indicative of the fact that it might be an unusual reactive phenomenon. [68] Verruciform xanthoma had also been reported in patients following bone marrow transplantation, with or without graft versus host disease. [69] Nevertheless, their patient did not have any associated dermatoses or systemic diseases.

- • Penile verruciform xanthoma typically manifests as an asymptomatic, solitary lesion, that measures between 2 mm and 10 mm in an otherwise healthy man, usually after the fifth decade of life.

- • Penile verruciform xanthoma may grow slowly over years or rarely, as in their reported case, demonstrate rapid growth in just a few months.

- • A review of previously reported cases had demonstrated that even though the pedunculated or sessile tumour upon the penis might manifest in a broad range of colours, from whitish or skin-coloured to pinkish-red and brown, it is usually associated with a yellowish hue, which may be regarded as an important clinical clue for the differentiation of penile verruciform xanthoma from other tumoral lesions, including mainly condyloma acuminatum. [22] [35] [42] [68] [69]

- Moreover, in some cases, verruciform xanthoma of the penis may be indurated and focally ulcerated, simulating malignancy.

- Even though the clinical differential diagnosis of verruciform xanthoma includes many benign and malignant conditions, its morphological characteristics and histopathology examination appearance with subepithelial foamy histiocytes are unique, and performance of a biopsy in suspicious cases is crucial to the diagnosis. [35] [42] [69]

- As genital occurrence is not a well-known feature of verruciform xanthoma, the diagnosis of penile verruciform xanthoma might be delayed, and some patients with penile verruciform xanthoma may receive incorrect or unnecessarily aggressive treatments.

- In the reported literature, penile lesions of verruciform xanthoma had often been described as wart-like papules/nodules with a "cauliflower-like" verrucous surface, whereas scrotal verruciform xanthoma may also manifest with "mulberry-like" papillomatous lesions. [23] Nevertheless, a combined morphology consisting of a pedunculated component upon a verrucous base, as in their reported case, had not been reported previously in penile verruciform xanthoma.

- Surgical excision of penile verruciform xanthoma lesions has remained the gold standard for the treatment of verruciform xanthoma, whereas superficial electrocauterization, carbon dioxide laser, cryotherapy, radiotherapy, topical steroids, and imiquimod have been utilised in select cases. [35]

- Given the benign nature of verruciform xanthoma, a wait-and-see approach is another option of management, especially in elderly patients, and it was the choice made by their reported patient in his case.

- Kobaner et al. [67] made the ensuing conclusions:

- Even though not common, verruciform xanthoma should be kept within the differential diagnosis for solitary tumoral penile nodules with a yellowish colour in elderly patients.

- It should be noted that verruciform xanthoma lesions might have an atypical clinical appearance of the described variants, such as showing two components.

Ekanayaka et al. [70] made the ensuing introductory iterations related to verruciform xanthoma:

• Verruciform xanthoma (VX) is a rare benign disorder which was first reported by Shafer in the oral cavity in 1971. [71]

• Verrucous epithelial proliferation and accumulation of foamy histiocytes within the dermal papillae are the hallmark of this lesion.

• VX demonstrates marked predilection for the oral mucosa.

• Extraoral lesions are much rarer and have been reported mostly in the genital skin, including the penis, scrotum and vulva. [23] [71] [72]

• A single case of VX had been reported on the nasal mucosa. [26]

• Nevertheless, cutaneous forms of VX had been reported within the extremities, axilla and breast.

Ekanayaka et al. [70] reported a 75-year-old man, who had manifested with a rapidly growing penile lesion of 3-months duration that was associated with mild itchiness (see figure 6). During his clinical examination, his prepuce was found to be unretractable and studded with multiple soft pinkish-red nodules of varying sizes, ranging from 0.5 mm to 15 mm in diameters. The outer skin of the prepuce had demonstrated a whitish ill

Figure 6: Multiple soft pinkish red nodules in the prepuce (before circumcision). Reproduced from [70] under the Creative Commons Attribution License. This is an open access article licensed under a Creative Commons Attribution-ShareAlike 4.0 International License. (CC BY-SA. 4.0), which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are attributed and materials are shared under the same license.-defined patch indicative of lichen sclerosus. His glans penis had a circumscribed pinkish-red warty plaque with yellowish borders measuring 20 mm in diameter, and this lesion had extended towards his urethral meatus. Another small yellowish papule was found along the corona of his glans penis. There was no ulceration or regional lymph node enlrgement. The results of his blood tests, including the lipid profile, were within their normal ranges. A clinical diagnosis of squamous cell carcinoma (SCC) was made, and an incision biopsy was obtained from one of the foreskin lesions for pathology examination to confirm the diagnosis. Microscopy examination of the biopsy specimen demonstrted regular epidermal hyperplasia, papillomatosis, hyperkeratosis and focal parakeratosis. Scattered foam cells were also visualised within the papillary dermis with chronic inflammatory cells within the upper dermis. There was no cellular atypia or evidence of malignancy noted during the microscopy examination. Subsequently, an excisional biopsy of a single lesion was undertaken, which demonstrated similar histopathology examination features including: parakeratosis extending along the rete-ridges, neutrophil exocytosis within the parakeratotic layer and characteristically, more prominent aggregates of foamy histiocytes within the papillary dermis (see figures 7 & 8). The foamy cells were noted to have exhibited periodic acid-Schiff (PAS) positive staining, diastase resistant cytoplasmic granules. The positive staining with the immunohistochemical stain CD68 and negative staining with AE1/AE3 had confirmed the histiocytic nature of the foamy cells and had facilitated the diagnosis of VX, excluding the possibility of carcinoma including a clear cell carcinoma (see figure 9). As the next step, circumcision was undertaken, and the features had confirmed the presence of multifocal VX. The adjacent tissue upon examination demonstrated evidence of lichen sclerosus. The involvement of both skin and mucous membranes of the penis was adjudged to be compatible with the diagnosis of multifocal mucocutaneous VX. A few lesions had remained within the glans penis following the circumcision (see figure 10).

Ekanayaka et al. [70] made the ensuing educative discussions:

- VX is an asymptomatic yellowish red to grey colour warty, papule, plaque or polypoid lesion.

- The size of the VX lesion does tend to range between 2 mm and 20 mm in diameter.

- Oral VX lesions are much common in middle-aged men and extra-oral lesions demonstrate a greater predilection for middle-aged to elderly men.

- Nevertheless, according to a study which was undertaken by Tamiolakis et al, VX could occur in a wide age range from 2.5 years to 89 years. [73]

- VX may clinically simulate many benign and malignant lesions, including: viral warts, condyloma acuminatum and verrucous or conventional squamous cell carcinoma. [23]. [74] [75]

- VX has usually tended to be solitary but VX may very rarely be multifocal. [10] [76]

- All the multifocal VX lesions which had been reported previously were in the upper aerodigestive tract.

- In 2014, Tang et al. had reported an unusual case of disseminated VX with oral, cutaneous and genital involvement, without an obvious underlying cause. [77]

- Furthermore, Tamiolakis et al. had reported that multifocality as a rare finding, and they had also reported a single case of disseminated VX. [73]

- VX has usually tended to be a sporadic lesion. [76]

- Recent studies had intimated that VX may demonstrate an association with chronic inflammatory conditions, systemic and metabolic disorders and benign and malignant neoplasms including lymphoedema, graft versus host disease, discoid lupus erythematosus, systemic lipid storage disease, lichen planus, lichen sclerosus, epidermal nevi, CHILD (congenital hemidysplasia, ichthyosiform erythroderma and limb defect syndrome) and in-situ or invasive SCC. [75] [76] [77]

- Their reported patient had demonstrated an association of VX with lichen sclerosus.

- The aetiopathogenesis of VX is yet to be determined, although many studies have claimed that this is probably a reactive process following epithelial damage. As this lesion shows an architectural resemblance to verrucous mucocutaneous lesions, human papilloma virus (HPV) has been suggested as a causative agent of VX. However, many studies have failed to detect HPV in VX lesions. Mohsin et al. proposed that damaged keratinocytes attract neutrophils and stimulate rapid epidermal growth (4). [26]
- Zegarelli et al. had suggested that VX may emanate from the release of lipids from degenerating keratinocytes pursuant to local damage due to irritation or trauma. [78] The released lipids are then engulfed by dermal macrophages, forming foam cells.
- The aforementioned concept had been strongly supported by a study which was undertaken by Tamiolakis et al. [73]. Therefore, it has been speculated that VX might be a unique reaction pattern to local irritation leading to recruitment and persistent accumulation of foamy histiocytes in the dermal papillae.
- Nevertheless, some authors had postulated different etiological mechanisms such as local immunological reactions and autoimmune processes. [23] [73].
- Overall, there had been insufficient evidence for a definite pathogenetic mechanism of VX to be fully established.
- VX is an exophytic lesion demonstrating marked hyperkeratosis, parakeratosis and acanthosis of epidermis with uniformly elongated rete-ridges and papillomatosis with flattened bases.
- Characteristically parakeratosis blends with the keratinocytes of deep rete-pegs.
- The presence of an intense neutrophilic infiltrate predominantly within the parakeratotic layer is another consistent feature of VX. [71] Nevertheless, the diagnostic feature of VX lesion is the aggregates of foamy histiocytes within the dermal papillae, characteristically limited to the papillary dermis.
- The base of the VX lesion demonstrates a plasma cell infiltrate of varying intensity. Most importantly, VX lesion demonstrates no cellular atypia.
- Surgical excision is the treatment of choice for VX while electrocautery CO2 laser, cryotherapy and radiotherapy are other options. [22] [43]
- Imiquimod, which is an immune response modifier, is usually utilised to treat genital warts, superficial basal cell carcinomas, and actinic keratosis, had also been demonstrated to be effective in some cases.
- Their reported patient was commenced on cryotherapy, which was being continued every three weeks. He had demonstrated gradual, but slow improvement during the four months of his treatment.

Ekanayaka et al. [70] made the ensuing conclusions:

- VX is an extremely rare case of multifocal mucocutaneous VX of the penis clinically mimicking SCC.
- To the best of their knowledge, their reported case, was the first case of verruciform xanthoma reported in Sri Lanka.
- Awareness VX and its diagnostic features does help to prevent the undertaking of unnecessary surgical interventions.
- Furthermore, considering the association of VX with malignant tumours, follow up is mandatory for the early detection of such complications.

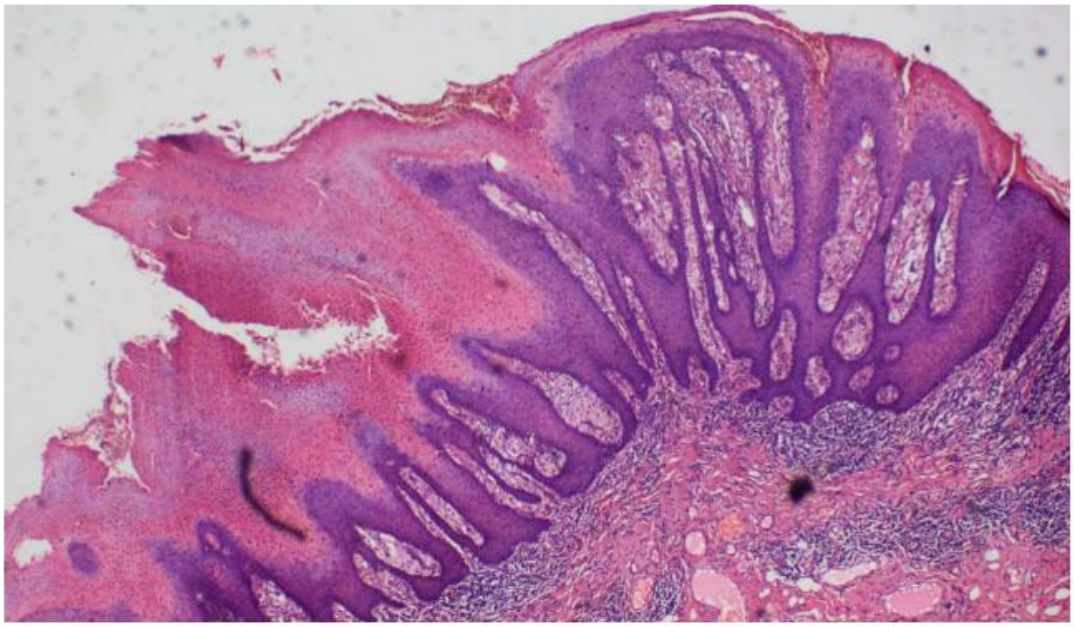

Figure 7: Epidermal hyperplasia, hyperkeratosis and parakeratosis extending along the rete ridges and aggregates of foamy histiocytes within the papillary dermis. (H& E x 40] Reproduced from: [70] under the Creative Commons Attribution License.

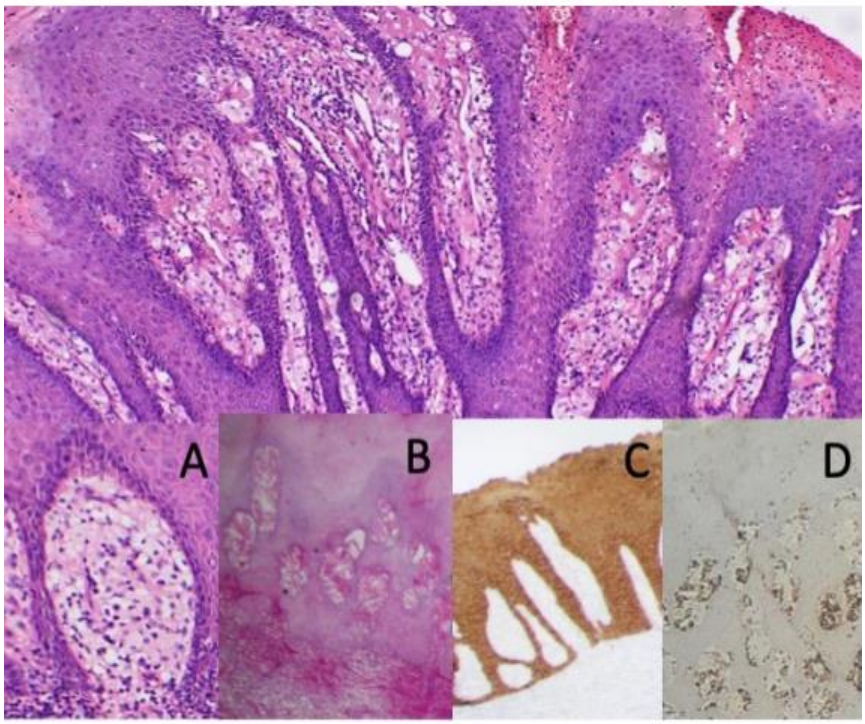

Figure 8: A Collections of foamy histiocytes within the papillary dermis and neutrophil exocytosis within the parakeratotic layer (H & E x400) B PAS-D C AE1/AE3 (IHC) D CD68 (IHC). Reproduced from: [70]

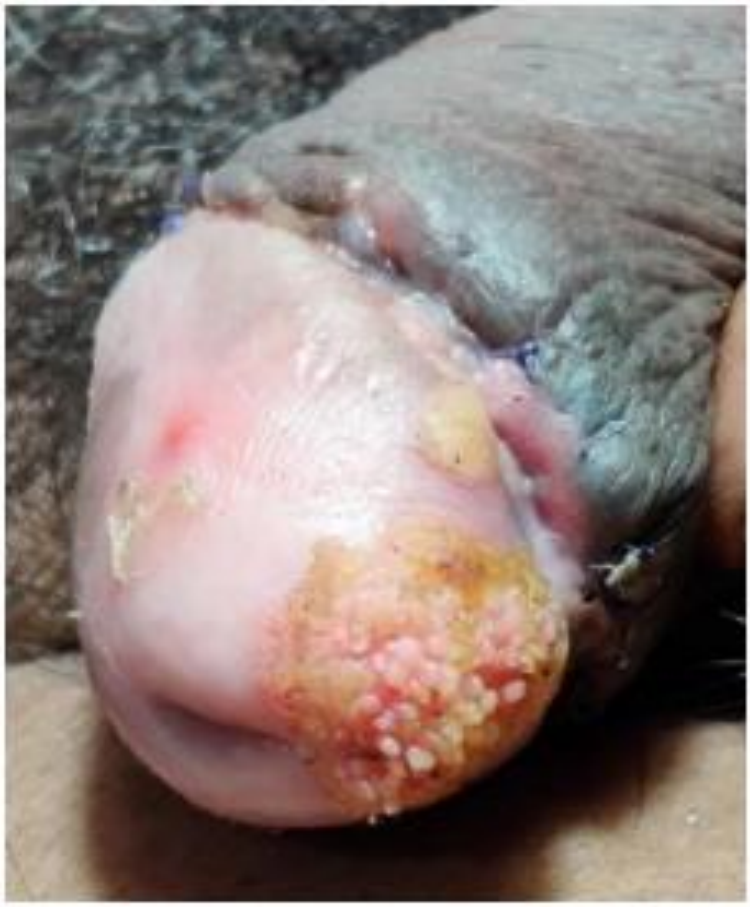

Figure 9: Lesions remaining in the glans after circumcision: Reproduced from: [70]

Frankel et al. [79] described the clinical and pathology findings of a 16-year-old girl who was afflicted by verruciform xanthoma of her vulva, the third such a reported case in an adolescent girl. They made the ensuing iterations and recommendations:

- It is important to recognize this uncommon clinical entity because it can simulate many other conditions, and the usual treatment modalities for wartlike growths upon the vulva (i.e., imiquimod, podophyllin, and trichloroacetic acid) are not effective.
- Wide local excision of the lesion does seem to be the only effective and curative treatment modality for verruciform xanthoma, as had been reported in the literature and is such with our case.

Erşahin et al. [80] stated the following:

- Verruciform xanthoma (VX) is an uncommon lesion with a predilection for oral mucosa.
- Only 16 cases of VX of the penis have been reported by 2005.
- Histologically, VX lesions in different locations are identical; nevertheless, the aetiology of VX is controversial.
- Previous studies had reported the presence of human papillomavirus (HPV) in VX of the skin.

Erşahin et al. [80] undertook a study in order to ascertain whether HPV is a causative agent in this rare case of VX of the penis. Erşahin et al. [80] reported that microscopically, the lesion had demonstrated prominent verrucoid squamous hyperplasia with hyperkeratosis, parakeratosis, and acanthosis. Histiocytes, a hallmark of VX, were identified in the elongated dermal papillae. Nested polymerase chain reaction was performed on the DNA with the commonly used primer sets MY9/MY11 and $GP5^{+}/GP6^{+}$, which identify more than 40 HPV types. The results failed to identify HPV DNA within the sample, even though HPV could be readily detected in genomic DNA extracted from paraffin-embedded condyloma acuminatum, a known HPV-associated lesion. Additionally, Erşahin et al. [80] tested a VX lesion of the palate for HPV DNA and obtained negative results. Erşahin et al. [80] concluded that their results had suggested that VX could arise without HPV infection and had indicated other possible origins may be involved. Erşahin et al. [80] made the ensuing discussions:

- Verruciform xanthoma (VX) is an uncommon lesion with a predilection for oral mucosa.
- VX was first described by Shafer1 in the oral mucosa in 1971. [36]
- Fewer than 50 cases of VX in extraoral locations had been reported, which included only 16 cases of VX of the penis.
- Most common extra-oral VX lesions that occur elsewhere arise upon the vulva, skin, and scrotum. [50] [72] [81]
- The first description of VX which had arisen upon the penis was reported by Kraemer et al in 1981. [39]
- Histopathologically, VXs of different locations demonstrate almost the same characteristics.
- As the name implies, xanthoma cells (foamy macrophages) within the submucosa or dermis are the hallmark of VX.
- The pathogenesis of this accumulation is not understood.
- Acanthosis, epidermal hyperkeratosis, papillomatosis, and a bandlike plasma cell dominant infiltrate at the base of the lesion are visualised.
- There is no epidermal atypia.
- The differential diagnoses of these histological examination features would include squamous carcinoma, verrucous carcinoma, and condyloma acuminatum.
- Koilocytosis within the upper epidermis that is found in condyloma is absent or inconspicuous in VX.
- In addition, characteristic foamy macrophages are not visualised in condyloma or squamous carcinoma and verrucous carcinoma.
- In VX the basement membrane is intact, and there is no evidence of invasion of the stroma.
- The aetiology of VX has remained controversial.
- Many groups had reported the presence of human papillomavirus (HPV) in VX of the skin, whereas others failed to detect HPV DNA in VX lesions.
- The purpose of their study was to ascertain whether HPV is associated with their case of VX of the penis.

Erşahin et al. [80] detailed out their case report as follows: The patient was a 71-year-old man of Italian origin, who had manifested with phimosis and a swollen, oedematous, and firm lesion which had involved his foreskin. His family denied him having any significant medical problems other than a history of mild stroke many years ago. He had a fine baseline tremor. His electrocardiogram demonstrated a Q wave in lead III that was consistent with a remote myocardial infarction; nevertheless, he did not have any history of cardiac problems according to his son. The VX was removed by surgical excision, which normally provides an excellent prognosis and appears to be more effective than cryosurgery. [81] Formalin-fixed, paraffin-embedded blocks of his excised penile lesions were sectioned at 5 μm and stained with hematoxylin-eosin, periodic acid–Schiff, acid-fast stain, and Grocott methenamine silver. Immunohistochemical analysis for CD68 was undertaken. Formalin-fixed, paraffin-embedded tissue of the excised lesions was processed as described by Shibata et al.7 Briefly, two 10-μm sections cut from paraffin block were placed in an Eppendorf tube and deparaffinized with sequential washes of xylene and 95% ethanol. The tissue pellet was desiccated by centrifuging under vacuum, resuspended in 200 μL of distilled water, and incubated for 10 minutes at 100°C. Fifty microliters of the supernatant was utilised for polymerase chain reaction (PCR).

Conclusions

- Verruciform Xanthoma of the penis is an uncommon lesion that afflicts the penis and in view of the rarity of the lesion it would be envisaged that the majority of clinicians all over the world would be unfamiliar with the diagnostic features of the lesion.
- Less than fifty cases of verruciform xanthoma of the penis had been reported in the literature which could be due to the rarity of the lesion or misdiagnosis of the lesion because the lesion simulates more common lesions of the penis.
- Verruciform xanthoma of the penis is a benign lesion which if diagnosed accurately, could be treated with less aggressive treatment procedures and would avoid the undertaking of mutilating surgical procedures.
- A high-index of suspicion is required to diagnose the lesion by the undertaking of biopsy of the penile lesions for pathology examination.

Conflict of Interest

Nil

Acknowledgements

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