Common clinical pattern of warts in children at Al- Jumhoria hospital

Benghazi - libya

This thesis is submitted to the dermatology department/ Benghazi university / Benghazi-Libya/in partial fulfillment of the requirement for the degree of Master in dermatology.

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Certification

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Declaration

This is to declare that I have not submitted this research work to any other university for the purpose of obtaining any post graduate degree in dermatology.

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List of abbreviations

HPV:Human papilloma virus.

PV: papilloma virus.

E region: early region.

L region: late region.

RBP: retinoblastoma protein.

LCR: long control region.

V.V : verruca vulgaris.

FEH: Focal epithelial hyperplasia.

BP: Bowenoid papulosis.

SCC: squamous cell carcinoma.

VIN: vulvar intraepithelial neoplasia.

BD: Bowen`s disease.

EGBD:extra genital bowen`s disease.

BCC: basal cell carcinoma.

NMSC: non melanoma skin cancer.

OTC: all over the counter.

CO2 laser: carbon dioxide laser.

5-FU: 5 Fluorouracil.

DCP:Diphencyprone.

SADBE: Squaric acid dibutyl ester.

summary

1-Summary:

Wart, or verrucae, are bengin proliferations of the skin and mucosa that are caused by human papilloma virus. They are one of the most common viral infection of skin and mucosal epithelium. Occur at any age but are more common in children and adolescents. Although not life threatening, it is common and it causes discomfort to children, anxiety to parents.

Therefore our objective was to study wart and to determine the most common clinical pattern in children and to correlate with number and duration of lesion, the most common affected site, age, sex, kobnerization, associated skin and systemic diseases and percentage to transemit within family.

Three hundred child with clinically diagnosis of warts all patients younger than fourteen years attending to outpatient department and cryotherapy clinic of AL- Jumhoria hospital -Bengahzi take history & examine patient as outpatient during a period of six months from March 2012. A detailed history have been taken and recorded according to prepared performa.

A complete dermatological examination was done, taking care to note the morphology, location, size and the distributon of the warts.

The collected data was statistically analyzed using the computerized program, chi-squared (X^2) test, with p value $\leq$ 0.05 considerd significant.

In our study, male to female ratio was 1: 1.3. Most of them in age between 6 and 10 years (50.7%) with minimum age of one month and maximum age of 14 years. Kobnerization was seen only in (2%) of patients included in this study .

Family history of same disease were positive (47.7%) of the patients (53.6%) were female patients and (40.2%) were male patients, this difference was

statistically significant p = 0.021.

History of other skin disease. were positive only in (2%) of the patients. History of systemic disease were positive in (4%) of the patients.

In our study nearly half of patitents had common wart 41.3% , planter wart constitute to 25.3%, filiform wart to 9.3%, plane wart was constitute to 11%.

Warts distributed all over the body, in this study most common site is feet (33.3%), while (26.7%) were found in hands, (21 %) were in face, (12.7%) seen in fingers, (2.7%) in knees (2%) forearm, (0.7%) in elbow,(0.3%) axilla and only (1%) in genital tract.

Lesions localized in one site represent (61%) of patients, while two sites constitute (37.3%) and three sites were (1.7%) of the patients.

Mean number of lesions were equal to 4.1 ± 3.9, about (74.7%) of the patients were suffering from 1 to 5 lesions, while (19.7%) of the patients had 6 to 10 lesions, (5.6%) had more than10 lesions.

Mean duration of warts was 8.5 ± 7.8 months, the minimum duration observed was one week and maximum duration was 3 years, in this study most of patient had disease duration ≤ 1 year (88%) while only (12%) of patient had disease duration >1year.

Moreover, (77.3%) of patient of disease duration ≤ 1year had ≤ 5lesions while (55.6%) of patient of disease duration > 1year had ≤ 5lesions, while (22.5%) of patients of disease duration with ≤ 1year had > 5lesions while (44.4%) of patients of disease duration > 1year had > 5lesions, this difference was statistically significant p value equal to 0.018.

Introduction

2-Introduction:

Warts, or verrucae, are benign proliferations of the skin and mucosa that are caused by infection with Human papillomaviruses (HPVs) (1). Researchs on papillomavirus (PV) began in the early twentieth century. In 1933, a PV was isolated as a possible etiologic agent of warts in rabbits. Since then, this class of viruses has been considered natural viral infectious agents responsible for the development of warts in different groups of mammals, including man. In 1935, Rous described the warts in rabbits as having the potential for malignant transformation (2). Moreover, Strauss et al. reported the first visualization of PV particles in human warts by means of electron microscopy in 1949 furthermore; in 1950, the carcinogenic potential of the HPV was discovered in patients with epidermodysplasia verruciformis (2). However the structure of the viral genome was only unveiled in1963 by Crawford & Crawford (3).

HPVS are tiny non-enveloped, double-stranded DNA viruses capable of infecting mucosal and cutaneous epithelium (4). They are the causative agents of a variety of benign and cancerous lesions of the skin and other epithelial surfaces. At least 189 HPV genotypes have been described (5). Most HPV types are associated with one or a few histopathologically distinct types of lesions and may be restricted to particular location on the body. HPV types 2,4 &27 are responsible for common warts *(*verruca vulgaris*)*, which are slightly raised rough surface epithelial proliferations that occur most often on the hands, but can also grow elsewhere on the body. Other types of warts include plantars warts (verruca plantaris) that occur most commonly on the soles of the feet and caused by HPV type1 (6). Flat warts (verruca plana) usually appearing on face responsible for these lesions are HPV 3, 10 & 38 (7). Butcher's warts of the hands and fingers caused by HPV7 (8), and oral, gential or anogenital warts *(*condyloma acuminata)*;* which are caused by HPV 6, 11, 16 & 18 (9).

Warts are spread by direct or indirect contact. Impairment of the epithelial barrier function by trauma including mild abrasions, maceration or both, greatly predisposes inoculation of virus (10).

Warts are common in children and adolescents with the greatest incidence of warts is noticed between 12 and 16 years of age; they are have been noted to occur with greater frequency in girls than boys (11).

Adults may also be affected by the virus resulting in similar symptoms. Hands, legs, face, inner areas of the mouth and the genital areas are some of the areas where warts may be observed (11).

Generally, in sites of viral replication and cytolysis, Increased numbers of inflammatory cells & lymphocytes, particularly cytotoxic T-lymphocytes (CTL), would be expected, however histological examination of skin warts and genital HPV lesions shows a lack of inflammatory cells (12).There is a decreased in the density of epidermal LC in many cutaneous(13) and mucosal(14). When the common warts regress spontaneously, infiltrating lymphocytes & macrophages are found & keratinocytes show evidence of cytopathic effects. Plane warts tend to regress readily than other warts,have a mononuclear cell infiltrate in the dermis consisting mainly of CD4 cells during regression(15).Recently mentioned clearance was characterized by an active cell-mediated immune response with an influx of T-cells & macrophages The T-cells were in both the stroma & the epidermis at a ratio of CD4:CD8 of about1:0.9, while in non regression warts the ratio was 1:15 (15).

Laboratory diagnosis of skin warts is usually unnecessary because they can be distinguished morphologically (16).

The most commonly used treatments for warts involve destruction of the area of epidermis infected with the virus. Such treatments may involve applications of topical

preparations or surgical approaches (17). Other therapies aimed at modifying the growth of epidermis or stimulating an immune response (17).

Literature review

3-Literature review:

The term wart refers to the non-cancerous growth of the top layers of the skin caused by a viral infection with Human papillomaviruses (HPVs) (11).

Etiology:

HPVs are small DNA viruses of the papillomavirus family. At least 189 distinct PV types had been described, of which 151 were found in humans on the basis of viral DNA analysis (5). A new HPV sub –type is defined when its DNA sequence is less than 90 percent homologous to all other known HPVs (18). The life cycle of an HPV is directly linked to cell differentiation program of the host cell. They cannot complete its replication cycle in cultured cells suggesting that differentiation of epithelia cells in tissues is important for HPV production (19), moreover replication appears to be synchronized with epithelial cell proliferation (20,21).

The main HPV types infecting the skin are distributed over five genera (alpha, beta, gamma, mu ,nu), and 16 species (4). The HPV types most frequently detected in warts belong to species of three genera (alpha, gamma and mu). Their viral genome is divided into three regions based on their location and functional properties. The early (E) and late (L) regions, which are known as (translation units), and a third region called long control region (LCR). The E region contains up to eight genes (E1 to E8), (E1and E2) are responsible for replication of the HPV, (E2) for DNA transcription, (E4) causes maturation and release of viral particls, (E5,E6,E7) cell transformation, and (E6,E7) immortalization, moreover E6/E7 genes also encode proteins associated with malignant lesions (22). These proteins stimulate cell proliferation interacting and suppressing the functions of cellular protein p53 and retinoblastoma protein (pRb),which are involved in controlling cell proliferation. Only the E6/E7 proteins of

high- risk HPVs are able to immortalize primary human keratinocytes, but not similar proteins of low risk HPVs.

The genes of the L region (L1 and L2) encode a major and a minor capsid proteins, respectively (23). They are contributes to the incorporation of the viral DNA into the virion (23). The LCR region is between L1 and E6 and has between 500 and 1000 base pairs. Progression time and type of lesion correlates with the quantity of viral particles detected. Younger warts present a higher viral amount when compared to old warts. Furthermore plantar warts have a higher viral load than common warts. However the center of the lesion appears to be the main site of viral concentration (24).

In benign lesions, replication of the viral genome is extrachromossomal, whereas in malignant lesions, although the viral DNA is integrated into the chromosomes of the host cell but there is no viral replication. There is inactivation of expression of the E2 protein, which acts as a negative regulator of the expression of the E6 and E7 oncogenes. The last two promote cell immortalization by inhibiting cellular proteins that regulate the cell cycle (p53 and pRB), which are critical for tumor suppression (24,25).

Incubation period:

Infection begins when the HPV reaches the cells of the basal layer; there is no viral replication at this location and the virus just keeps its genome by amplification of a low number of copies. The replicative phase and protein synthesis occur in the suprabasal differentiated keratinocytes (24,25). They are may persist in a latent and sub clinical forms and may be subsequently reactivated. Subclinical and latent HPV infection it has been estimated up to 70% of genital HPV infections, although; unnoticed by the patient but detectable by full clinical examination, histology,

cytology or molecular analysis i.e. a latent infection, there may be no morphological changes but the viral DNA present (17).

Acquisition of HPV depends on several factors, including the location of lesions, the quantity of infectious virus present, the degree and nature of the contact, and the general and HPV-specific immunologic status of the exposed individual (26,27).

The time of acquisition of the infection can seldom be ascertained for common and plantar warts, but the incubation period has been estimated to range between a few weeks and more than a year (28). experimental infections have taken as long as 20 months to produce clinical warts (29).

Mode of transmission and risk factors:

Verrucae are spread by direct skin-to-skin contact or indirectly via contact with contaminated surfaces such as swimming pools or communal showers (30). However having a family member with a wart has been shown to be stronger risk factor to the child than the use of swimming pools and shared bathing area (31). Persons who walk barefoot often are at increased risk of plantar warts (32). Moreover, meat handlers are at risk of hand warts (33), and nail biters commonly have multiple periungual warts (34). Immunosuppression is another important risk factor. An observational study of immunosuppressed patients at least five years after receiving a renal transplant found that 90 percent of patients had warts (35). Once HPV has infected skin autoinoculation can occur by scratching, shaving or traumatizing the skin (36,37). Iatrogenic transmission can be occur but because of long incubation period, iatrogenic spread would be difficult to establish, although the possibility exists because HPV DNA has been detected on instrument used for the examination of women with clinical or sub clinical infection (38,39).

Epidemiology:

Warts are very common viral infections, with an estimated incidence of 7 to 10% in the European population and 1% in the U.S. population (40).

Although warts occur at any age, they are unusual in infancy and early childhood. The incidence increases during the school years to reach a peak in adolescence and early adulthood (41,42). The greatest incidenceis has been reported between 12 and 16 years of age. Warts noted to occur with greater frequency in girls than in boys (43).

Clinical feature:-

1. Benign cutaneous lesion:

1.1.Common wart (verruca vulgaris):

Verruca vulgaris (VV) are rough surface papule or nodule which may be single or multiple, they are usually asymptomatic but may be tender on the palmer aspects of the finger, when fissured or when growing beneath the nail plate (17). Confluence of lesions can form large masses. Although, common wart can occur in any part of the body, they are more common on the back of hands and fingers (44). A frequent location in children is the knee (17).

VV around the nail folds or beneath the nail called periungeal form is generally painful and, frequently, produce dystrophy and deformity of the nail (45).

VV on the eyelids has been reported may be associated with conjunctivitis or keratitis (17).

Appearance of common warts on or around the genitalia account for only 1 or 2% of the cases; in the male they are almost always confined to the shaft of the penis. They often retain their usual morphological characteristics with dry hyperkeratosis and frequently do not resemble soft condyloma acuminate (genital warts) (17).

Butcher`s wart they owe their name as they are observed in butchers, fish and poultry handlers (30). They are extensive verrucous papules or cauliflower in the shape of the hands and fingers and caused by HPV7 (45).

The types of HPV most involved in lesions of (VV) are: HPV 2 (25,46), HPV 27, HPV 57 (46,47) (HPV types closely related to HPV2), HPV 4 (25,48) and HPV1 (49,50).

About 65% of common warts disappear spontaneously within 2 years. Neither the patient's age nor the number of warts present influences the course (51,52).

Regression of common warts is asymptomatic and occurs gradually over several weeks, usually without hyperpigmentation (52,53).

Malignant change in common warts is extremely rare but has been reported (17).

1.2. Planterwart:

Planter wart frequently caused by HPV1, however, these it occasionally inoculated with HPV type 4 (54). Trauma plays an important role in the inoculation of the warts, as the most commonly affected sites are the heel and the heads of the metatarsi (54). They are manifest as single or multiple lesions. When developed superficially, forming hyperkeratotic plaques, they are called mosaic warts, which are less painful and usually caused by HPV 2 (55), whereas, if lie deep, they are known as myrmecia, which are commonly painful and caused by HPV1(2).

The main differential diagnosis between plantar warts and plantar callus is important because the two disorders are frequently confused in clinical practice (56).

Planter warts can appear in areas that experience less pressure, such as the arch of the foot, this location, however, is not common for calluses, which are produced as a consequence of pressure on the skin. A clinical maneuver for distinguishing warts from calluses is tangential scraping; in calluses, the detachment of multiple

hyperkeratotic layers with a clean central fundus is observed, whereas warts present a multilobulated aspect above the superficial hyperkeratotic layer, accompanied by multiple black dots that correspond to thrombosed capillaries. In contrast, warts are indicated by certain dermatoscopic signs, such as black to red dots, globules corresponding to dilated and thrombosed capillaries of the papillae and interrupted dermatoglyphics in the lesion. Calluses present a translucent central corn or a homogeneous opacity (56). The use of the dermatoscope is useful and more sensitive than the naked eye (56).

1.3. Flat wart:

Flat warts are caused by HPV 3 and 10 (54). They are common in childhood, although, it is very rare in male adults and has been described in the context of HIV infection (57). The most commonly affected area is the face, followed by the back of the hands and the shins (54). The aspect is that of a papule or slightly elevated flat plaques with low desquamated (smooth surface). Coloration ranges from light brown to the color of the individual's skin, thus making flat warts hard to detect with simple inspection. Histologically, flat warts are characterized by less acanthosis than common or plantar warts, morever papillomatosis is minimal or absent (54).

1.4. Filiform wart:

It is a morphological varient of the common wart and the HPV types found appear to be the same found in lesions of common warts, especially HPV2 (17). Clinically they present as isolated or multiple lesions with the special filiform or elongated morphology, with a narrow pedicle and pronounced digital projections on the surface because of these projections they are called digitiform papillom, affecting mainly the face and neck. The main differential diagnosis is with acrochordons, which can have a similar morphology but are differentiated by their smooth surface (they lack digital

projections). The histological peculiarity of filiform warts is that the papillae are more elongated than those of common warts (54).

1.5. Pigmented wart:

Egawa was the first to describe these subtypes in 1988 (57). Although common warts and molluscum contagiosum can transform to a black color , in their involutionary phases, pigmented warts are pigmented from the initial phases (59,60). They are fundamentally located on the hands and feet (61). histopathologically, they present specific homogeneous cytoplasmic inclusion bodies (2). The HPV types detected in lesions are HPV4,60 and 65 (61).

2. Epidermodysplasia verruciformis :

Epidermodysplasia verruciformis (EV) is a rare disorder, usually autosomal recessive, with defect in cellular immunity and high susceptibility to skin cancer induced by HPV. The association between HPV and cancer was first recognized in the 50s among patients with EV, however patients with EV are highly predisposed to infection by a specific group of HPVs and at a high risk of developing cutaneous malignant tumors, resulting from the oncogenic effects of the viruses (62). The skin lesions appear early in childhood and are polymorphic; they are indistinguishable from flat warts when present on the face and neck, and scaly hypo or hyper-pigmented erythematous macules, similar to versicolor, when present on the trunk and limbs, moreover Thicker, pink or violet plaques, similar to seborrheic keratosis, are also found (2).

Malignant transformations generally begin in the fourth and fifth decades of life and predominate in sun-exposed areas, suggesting an important role of ultraviolet radiation. Although premalignant lesions such as actinic keratoses and malignant

lesions such as Bowen's disease and invasive squamous cell carcinoma are observed, basal cell carcinoma is rare in these patients (63).

The HPV types found in lesions of patients with EV are referred to as HPVs associated with epidermodysplasia verruciformis (HPV-EV). The HPV-EV types most commonly found in lesions of patients with EV are 5, 8, 9, 12, 14, 15, 17, 19-25, 28, 29, 36-38, 47, 49 and 50.

However HPV 3 and 10 are detected in the flat warts of these patients, similar to the general population.

Whereas HPV 5& HPV 8, is the most commonly found in malignant lesions. HPV 14, 17, 20 and 47 are less frequently found (63,64,65).

3. Benign mucosal lesions:

3.1. Focal epithelial hyperplasia:

Focal epithelial hyperplasia (FEH) or Heck's disease is a rare disease of the oral mucosa. It has a benign course and is associated with HPV type 13 and 32 (66). It is more common in children and women and presents clear racial predominance, being more common among American Indians, Eskimos and some African communities. It is clinically characterized by multiple small papules, pinkish in color, individual or forming plaques. Its lesions are asymptomatic and prone to spontaneous regression. The most common location is the lower lip, less frequently in the upper lip, tongue, oral mucosa, orophyarnx, plate and the floor of mouth (2).

3.2. Condylomata acuminata:

The most common manifestations of HPV in the genital area are anogenital warts or condylomata acuminata (64). They are often asymptomatic, but may cause discomfort, discharge or bleeding, the typical lesion is soft, pink, elongated and sometimes filiform or pedunculated similar to cauliflower, usually multiple especially

on moist surfaces (67). The low-risk HPVs, are HPV 6 and HPV 11, they are the most detected in lesions of condylomata acuminata. High risk HPVs such as HPV 16 and 18, while other HPV types can be found isolated or more often coinfected with HPV 6 and 11(67). The Buschke-Loewenstein tumor giant condyloma acuminatum or verrucous carcinoma of the anogenital region, is a clinically aggressive tumor, with ulcerated cauliflower-like lesions, with fistulas and abscesses.

Usually associated with HPV 6 and 11 they present as in exophytic and endophytic growth. Although it present with local invasion and high recurrence rates, metastases are very rare, and histologically, it is a benign tumor (69).

Genital warts in children

Anogenital warts are uncommon in children (17). Although discovery of external genital warts in children often raises possibility about sexual abuse (70).

Infection from the mother's genital tract at delivery is regarded as a frequent source of childhood anogenital warts, probably including those presenting up to 2 years of age (71,72). However genital papillomaviruses transmitted from mother to baby at birth may persist in childhood (73,74).

Postnatally, transmission from adults with genital warts may occur non-sexually, such as by sharing a bath with an infected adult (75).

3.3. Bowenoid papulosis:

The term bowenoid papulosis (BP) refers to multifocal papular lesions on the genitalia with histological features similar to squamous cell carcinoma (SCC) in situ or Bowen`s disease (BD). Clinically BP is characterized by multiple brownish or erythematous papules located in the anogenital region, affecting mostly young adults with an active sexual life (64). Clinically, BP must be differentiated from seborrheic keratosis, melanocytic nevus and common warts. BP is strongly associated with HPV

type 16 (64), however, other types of HPV such as HPV 18, 31-35, 39-42, 48 and 51-54 have been detected in lesions of BP (76).

Despite the histological atypia and association with high-risk HPV types, the course of BP in males and in young individuals is usually benign, with spontaneous regression occurring in many cases. However in females, the association with cancer of the cervix suggests a less benign course. Moreover, in the elderly and immunocompromised patients, its evolution also tends to be more aggressive (64).

4. Malignant mucosal lesions:

4.1. Bowen`s disease of the genitalia:

Carcinoma in situ or Bowen`s disease (BD) of the genitalia is associated with high-risk HPVs, especially HPV 16 (77). Clinically, it presents as a plaque, usually single, without tendency to spontaneous regression and with potential to progress to SCC (2).

4.2.Vulvar cancer:

Invasive vulvar cancer is usually preceded by vulvar intraepithelial neoplasia (VIN) or cervical carcinoma and often develops from long-course genital warts. Detection of HPVs in vulvar cancer is much lower than that of cervical carcinoma (2), they are ranges from 30% to 70% (77). Most observed type in vulvar carcinomas is HPV type 16 (2).

4.3. Penile cancer:

Clinically, the lesions present as ulcerated nodule or verrucous surface. The detection of HPV in lesions of penile cancer reaches 40-70% positivity and the most frequent type is HPV16 (79).

4.4. Anal cancer:

HPV is detected in approximately 80 to 96% of anal cancer lesions. Although the most frequent types of HPVs isolated from lesions HPV16, HPV 18 & HPV33 (78).

4.5.Cervical cancer:

A causal relationship between HPV and cervical cancer is observed in about 90% to 100% of the cases (80). HPV types 16 and 18 are the two most important carcinogenic types and account for about 70% of cervical carcinomas and 50% of intraepithelial neoplasia grade 3. HPVs 31, 33, 35, 39, 45, 51& 52 have also been detected in lesions of cervical cancer (81).

5. Malignant skin lesions:

5.1. Bowen's disease:

Bowen's disease (BD) is a squamous cell carcinoma in situ that occasionally progresses to invasive carcinoma. HPV infection, particularly the high-risk mucosal types, are frequently found in lesions of extra-genital Bowen's disease (EGBD), especially in the periungual region, on hands and more rarely on feet. The detection of the virus in these locations suggests autoinoculation from genital lesions (82).

The role of HPV is well established in genital BD, but is not fully clarified in its extra-genital forms (83).

High-risk HPVs are also found in lesions of EGBD in the absence of genital lesions (83). Other types of HPV have been detected in EGBD, such as HPV 2, low-risk mucosal HPVs 6 and 11 and HPV 54,58,61,62,73 (83).

5.2. Basal and squamous cell carcinomas:

The exact role of HPV in the development of non melanoma skin cancer (NMSC) like; squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), is not yet fully defined (84). Growing evidence suggests that HPV has important potential in the process of skin carcinogenesis (84,85,86).

The association between HPV and NMSC is observed both in immunocompetent patients and immunocompromised individuals, moreover, positive detection of viral

DNA in lesions is higher and presence of varied types of HPV in the same lesion is more frequent (64,85,87).

Differential diagnosis:

A history of increasing in number of acquired, grouped lesions is suggestive of warts (1). Dilated capillaries in the wart which bleed subsequent to peeling of the hyperkeratotic surfaces (87), help to differentiate warts from calluses (36,37). The different diagnosis varies considerably with the type of lesions and the site of involvement (1). Papules of lichen planus may resemble flat warts; the former may be differentiated by their color, polygonal shape, wickham`s striae, and buccal involvemen (1). Acrokeratosis verruciformis are characterized by verrucous papules on the extremities (1). Warts in epidermodysplasia may resemble pityriasis versicolor but are not transient (1). Penile and vulver warts may resemble nevi, benign keratoses, cysts, or ectopic sebaceous glands (1). Syphylatic condylomata must also be kept in mind in the differential diagnosis of anogenital warts (1). Amelanotic melanoma must also be cosiderd in a persistent wart (87).

Histopathological characteristics of cutaneous warts:

The histopathological characteristics of viral warts are papillomatosis, hyperkeratosis with prominent parakeratosis, hypergranulosis and acanthosis (89).

The rete ridges of common warts are elongated and at the periphery point radially toward the lesion (arborization). The most important characteristics in distinguishing common Warts from other papillomas are:

a) koilocytes which are small vacuolated cells with small round strongly basophilic nucleus surrounded by a clear halo and pale cytoplasm, located in the outer stratum spinosum and stratum granulosum; they represent the viral cytopathic effect.

b) straight up rows of parakeratosis,

c) foci of keratohyalin granules. These three changes are evident in young or active common warts (89).

Histopathological examination would help in identifying different viral types.

Flat warts show hyperkeratosis and acanthosis, however, papillomatosis and areas of parakeratosis are not less prominent, with only a slight elongation of rete ridges being observed. There is diffuse vacuolation and increase in cell size with centralization of nuclei that become strongly basophilic and pyknotic in the spinous and granular layers. Superficial palmoplantar warts (mosaic) present histopathological aspects similar to common warts. Which deep palmoplantar warts (myrmecia), are characterized by presenting, in the granular and spinous layers, abundant keratohyalin granules and eosinophils forming irregular inclusion bodies in the cytoplasm of keratinocytes (44,89).

Diagnosis:

The clinical appearance and history of acquired, slowly enlarging papules usually lead to diagnosis of viral wart (1). Application of 3% to 5 % acetic acid to genital warts enhances visualization of these lesions (1). Clinical diagnosis of warts is often sufficient, however atypical, subclinical or dysplastic lesions may need laboratory confirmation of HPV infection (17). The diagnosis of HPV infection is made by histopathology of lesions (45), or detection of viral DNA in infected cells (90). Hybridization techniques and polymerase chain reaction (PCR) methods used for HPV detection (2).

PCR is the most sensitive method and the most widely used for viral detection with its main application is related to situations where the amount of DNA available is limited(2).

DNA hybridization on tissue extracts or in situ are also used for HPV detection.

Among the hybridization techniques used are the following:

1) Southern blot which has high specificity and sensitivity.

It allows estimates of the amount of DNA in the lesion. It has limitations due to the high diversity of types of HPV, since it does not detect the DNA of unknown viral sequences (64).

2) Dot blot and reverse blot are laborious techniques that present similar sensitivity and good accuracy (64,90).

3) In situ hybridization uses radiolabeled probes and allows for topographic localization of viral DNA in cells and tissues. Although the sensitivity of this technique is limited, it is the best method to assess the distribution of HPV in lesions and it allows for viral localization by means of other markers (64).

4) Non-radioactive hybrid ca, this technique is safe, easy to perform. It presents good accuracy for mucosal lesions (64).

Treatment:

No single treatment is fully effective in all patients, different types of warts may need different site- dependent treatments, and treatments may need to be combined (91); therefore management of warts depends on the degree of physical and emotional discomfort, the extent and duration of lesions, the patient`s immunologic status, and the patient`s desire for therapy (91).

The best clinical guide to cure is the restoration of normal epidermal texture including the epidermal ridge pattern (51).

1. Hypnosis Therapy:

It is suggestion therapy could stimulate the immune system during therapy for wart (92,93).

1.1.Garlic extract:

Components of garlic (Allium sativum) have been shown to have antiviral activity and to inhibit cellular proliferation of virally infected cells (94,95) .

1.2. Duct Tape:

Occlusive duct tape treatment was championed by Dr. Jerome Litt in a 1978 article (96). Patients which used duct tape distant warts that were not treated with the duct tape also resolved, raising the possibility that the host's immune system was stimulated through local irritation produced by the duct tape. There were no reported side effects with using the duct tape, and most warts resolved within 1 month of treatment (97). This is an optimal approach to treating children with warts, because it is painless and cost effective (98).

2. Destructive Therapy:

These range from surgical curettage to cautery to caustic chemical ablation, and from cryotherapy to hyperthermic therapy. Many of the following approaches may be used with most warts, however, some warn against using destructive approaches for flat warts due to their tendency to Koebnerize (91).

2.1. Surgical removal by curettage or cautery:

Surgical excision and cautery of warts is not recommended as a standard therapy Moreover, like any destructive therapy, there is no assurance that the wart will not recur (98).

2.2. Chemical Cautery:

2.2.1. Silver nitrate:

Sliver nitrate is probably most widely recognized in its historical use to prevent conjunctivitis in newborns, however, in recent times it has largely been supplanted by

antibiotic eye drops(98). The use of silver nitrate has also been used to chemically cauterize epithelial tissues in the treatment of pyogenic and umbilical granulomas, epistaxis, corns and warts (98). Clinical application should be done with caution to avoid excessive burns and irreversible tissue staining. Clinical efficacy is moderate with a clearance was achieved in 43% and improvement in an additional 26% after 1 month by application of silver nitrate three times over 9days (71).

2.2.2. Monochloracetic acid, trichloracetic acid:

Monochloracetic acid, trichloracetic acid and are highly irritant chemicals can be used with effect but may cause painful reactions. In treatmentof genital warts (71).

2.2.3. Salicylic Acid:

Salicylic acid is a first-line therapy that many patients choose (98). It is a keratolytic therapy with a mechanism of action that slowly destroys virus-infected epidermis and may cause an immune response from the mild irritation caused by the salicylic acid (91). It is prepared in concentrations from 10% to 60% (98). Disadvantages are that results require weeks to months of treatment, and the patient must strictly adhere to the instructions (36,37).

Side effects are uncommon include occasional contact dermatitis due to colophony in the collodion base (98). Moreover there is also a potential risk of systemic toxicity in children that can be avoided if lower concentrations or limited areas of treatment are used (98).

2.3. Cautery/electrocoagulation:

Usually use in combination painful or resistant warts, but carry a risk of scarring. Topical application of mixture of local anaesthetics (EMLA cream), local anaesthetic injection or even general anaesthesia would be required for

keratinized skin,. A technique of blunt dissection has been advocated for plane warts (99).

2.4. Cryotherapy:

It is considered a second-line therapy (98). The effect on wart clearance may be through necrotic destruction of HPV-infected keratinocytes or by inducing local inflammation that an effective cell-mediated response (91).

3.Virucidal1therapy:

Glutaraldehyde is virucidal and available as a 10% water miscible gel or alcohol solution (98). Application of glutaraldehyde is typically applied twice a day and can stain the skin brown, as well as cause contact sensitivitty (98).

3.1. Formaldehyde:

Formaldehyde is also virucidal and works by disrupting the upper layer of epidermal cells and possibly damaging the virions (98).

3.2.Formic Acid:

Formic acid is the chemical irritant found in the stings and bites of many ymenopteran insects, including bees and ants, and was first isolated from red ants (98).

3.3.Antiviral Drugs:

Cidofovir is a nucleoside analogue of deoxycytidine monophosphate that inhibits DNA synthesis, induces DNA fragmentation, reduces epithelialization and enhances excoriation (98). It has been used successfully in HIV-positive patients for the topical treatment of genital warts (98).

4.Photodynamic therapy:

has been applied to warts in sensitive mucosal tissues including venereal warts and cervical intraepithelial neoplasia (CIN) in the vulva, penis and urethra and to oral and

respiratory tract papillomas (98) Generally, results are equivalent to or superior to other treatment modalities with the advantage that little, if any, scarring results. Additionally, the photosensitizers fluoresce which can assist in the pretreatment localization of lesions (98).

5.Lasers:

5.1.Carbon Dioxide laser:

The Carbon dioxide laser ($CO_{2)}$ lasers emit infrared light (10,600 nm) that is absorbed by water. Nonselective thermal tissue destruction results. A focused CO_2 laser beam can be used as a scalpel to excise the wart down to the subcutaneous tissue after which the base of the wart is vaporized by a defocused beam until a clean surgical field is obtained (98). This treatment may be useful for periungual and subungual warts that are recalcitrant to other treatments(91).

5.2. Neodymium: YAG laser :

The Neodymium:YAG Laser Nd:YAG lasers principal emission wavelength is at 1064 nm, still in the infrared range. Hyperthermic treatment with this laser has been reported to cause remission with no recurrence in several case reports (98).

5.3. Pulsed dye laser:

Treatment with a vascular lesion laser, also known as pulsed dye laser therapy, can selectively target hemoglobin contained in blood vessels within the wart (91).

6. Antimitotic Therapy:

6.1. Bleomycin:

Bleomycin is a chemotherapeutic agent, inhibits DNA synthesis in cells and viruses. Bleomycin is an alternative therapy for warts that have not responded to other therapies or warts that may be difficult to be surgically excise. Bleomycin comes in

15-unit vials; it typically is diluted with 30 mL of saline, and 0.3 mL (0.15 units) are injected into the wart (100).

6.2. Retinoid:

Retinoic acid topically useful in treatment of plane warts, although the best results are claimed for higher than usual concentrations and irritation is common (72).

6.3. Podophyllin and podophyllotoxin:

Podophyllin is a plant derived containing several cytotoxic compounds in unpredictable ratios (17). They are used in the treatment of anogenitalthey are more effective on mucosal than keratinized surfaces, they act as antimitotics, 0.5% in ethanol applied twice daily for 3 days, extending treatment to 4 or 5 days if necessary and if tolerated, gives better results than podophyllin, with cure rates between 60 and 70% (17).

7. Immunotherapy:

7.1. Imiquimod:

Topical immunomodulation, used as a 5% cream is currently licensed for treatment of genital warts (17).

7.2. Fluorouracil (5-FU):

In study, up to 70% of warts complete responsed when treated with 5-FU combined with lidocaine to reduce pain and epinephrine to induce vasoconstriction in order to sustain high local drug concentrations (98).

7.3. Contact Sensitizers:

The mechanism of action for topical immunotherapy with contact sensitizers is proposed to be a type IV hypersensitivity reaction (98).

Dinitrochlorbenzene has been used to elicit a repeated contact sensitivity reaction at

the site of warts and to induce clearance (17).

7.4. Intralesional injection of Candida or Mumps Antigen:

Intralesional immunotherapy employs the ability of the immune system to recognize certain viral and fungal antigens. Candida skin test antigen generally is used, it is believed that the delayed-type hypersensitivity reaction induced by these antigens increases the ability of the immune system to recognize and clear HPV, moreover, complete clearance of all warts distant from the injection site was noted (101).

7.5. Intralesional Injection of Interferon:

Intralesional injection of interferon used for genital warts that are recurrent or recalcitrant to other treatments, because found leukocytic interferon can both kill viruses and stimulate the immune system (98).

8- HPV vaccines:

The Food and Drug Administration (FDA) has approved two vaccines to prevent HPV infection: Gardasil and Cervarix, both vaccines are highly effective in preventing infections with HPV types 16 and 18, two high-risk HPVs that cause about 70 percent of cervical and anal cancers. Gardasil also prevents infection with HPV types 6 and 11, which cause 90 percent of genital warts (102).

Objectives

4-Aim of study:

Warts are the commonest viral infections which are encountered in the dermatological practice.

Our study aim to determine the most common clinical patterns of warts among children, below age fourteen attending to dermatology department and cryotherapy clinic at Al- Jumhoria hospital.

Patients & Methods

5- Patients and methods:

This is a cross-sectional study including three hundred child with age less than fourteen years. With clinically diagnosis of warts attending the out patient clinic and cryotherapy clinic at AL-Jumhoria hospital in Bengahzi city- Libya. during a period of six months from March 2012.

A detailed history of the patients age, sex, duration of the warts, personal and family history of cutaneous warts and personal history of associated skin and systemic diseases. All patients subjected to dermatological examination including: morphology, location, size and number of lesions and the presence of kobner phenomenon.

Data were recorded according to the prepared performa. At the end of the study, the collected information was statistically analyzed using the computerized program, chi-squared (X^2) test, with p value ≤ 0.05 considerd significant.

Proforma:-

Patient No:-------Name:----------

Age:----------Sex:--------

Associated skin diseases:----------

Associated systemic diseases:----------

Family history : Yes ( ) No( )

Degree of relation----------

Type of lesions : 1.Common wart.

2.plane wart .

3.Filiform wart.

4. plantar wart.

5.Anogantal wart.

Duration:----------

Number of lesions:----------

Site involved : Face ( )

Arms ( )

Trunk ( )

Legs ( )

Genitalia ( )

Other ( )

Secondary Changes:-Infection ( ) Necrosis ( ) Others ( )

Result

6-Result:

The study included 300 child with clinically diagnosis of warts, 168 (56%) of them were females and 132 (44%) were males as in (Fig.1) , with a male to female ratio of 1: 1.3. Their mean age were 8.1 ± 3.2 years, with minimum age of one month and maximum age of 14 years, 152(50.7%) of them were in age between 6 and 10 years while only 1 (0.3%) were less than one year and 81 (27%) were aged more than 10 years (Fig.2).

Kobnerization was seen in 6 (2%) of the patient under the study (Fig.3-Fig.4).

Family history of warts were positive in143 (47.7%) of the patients (Fig.5).

Family history of wart was seen in 90 (53.6%) of female patients and in 53 (40.2%) of males patients this difference was statistically significant $p = 0.021$ (Fig.6).

History of other skin diseases were positive in 6 (2%) of the patients as shown in (Fig.7), under study had systemic diseases and this including bronchial asthma seen in5(41.8%) of those cases, diabetes mellitus in 2(16.7%), while epilepsy, urinary tract infection, glomerular nephritis, ataxia telangectasia represent 1 (8.3%) for each as in (Fig8a, 8b).

The most common type of wart in the study was common warts (Fig.9), which was observed in 124(41.3%) of the patients, while planter wart seen in 76 (25.3%) (Fig.10), plane wart seen in 33 (11%) (Fig.11), filiform wart seen in 28 (9.3%) of the patients (Fig.12a-12b and12c) and 1 (0.3%) for each of the following types; {mucosal (Fig.13), periungual (Fig.14), mosaic pattern of planter wart (Fig.10), kissing wart (Fig.15) and genital wart (Fig.16)}.

The most common combination was between common and filiform warts which has been seen in 16 (5.3%) of the patients (Fig.17).

Figure 18 show the distribution of the patients according to the site that has been infected by warts, feet were involved in 100 (33%) of the patients, hands were found in 80 (26.7%), face in 63 (21%), knees and forearm in 13(4.3%), while elbow and axilla involved in 3 (1%) of the patients. However only three patients had genital wart (1%).

Lesions localized in one site represent 183 (61%) of the patients, while two sites constitute 112 (37.3%) and three sites were seen in 5(1.7%) of the patients(Fig.19). There was no statistically difference between males and females patients with regard to the type of wart & site involvement (Fig.20 - Fig.21).

Number of lesions ranged from one to thirty, mean number 4.2 ± 3.9. About 223 (74.3%) of the patients were suffering from 1 to 5 lesions, while 59 (19.7%) of the patients had 6 to 10 lesions and 18 (6%) of them had more than10 lesions (Fig.22).

Mean duration of warts was 9 ± 8.8 months, the minimum duration was one week and maximum duration was 3 years, in this study duration of the warts ≤ 1year constitutes to 246(82%) and duration of the warts >1year constitutes 54 (18%) of the patients (Fig.23).

Among patients with disease duration ≤ 1year 191 (77.6%) had ≤ 5lesions, while 55 (22.4%) of them had > 5lesions.Where as patients with disease duration > 1year had 32 (59.3%) of them had ≤ 5lesions, while 22 (40.7%) had > 5lesions and this difference was statistically significant (p value=0.014) (Fig.24).Figure 25 show distribution of the patients under study according to the duration of their disease and the number of sites involved.

One hundred fifty eight (64.2%) of the patients had single site involved in duration ≤ 1 year, 87(35.4%) of the patients had two sites while 6 (2.2%) had three sites involved.

While 25 (46.3%) of the patients with disease duration > 1year had single site involved, 25(46.3%) of the patients had two sites, while 4 (7.4%) had three sites involved and this difference was statistically significant (p = 0.0001) (Fig.25).

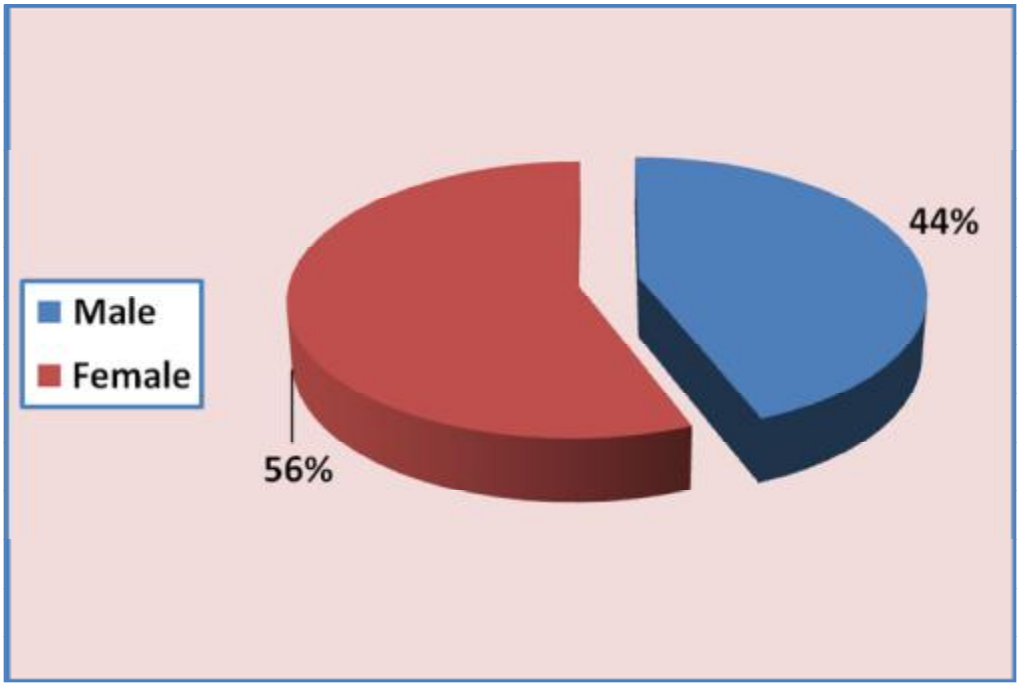

Fig.1:Distribution of the patients according to sex.

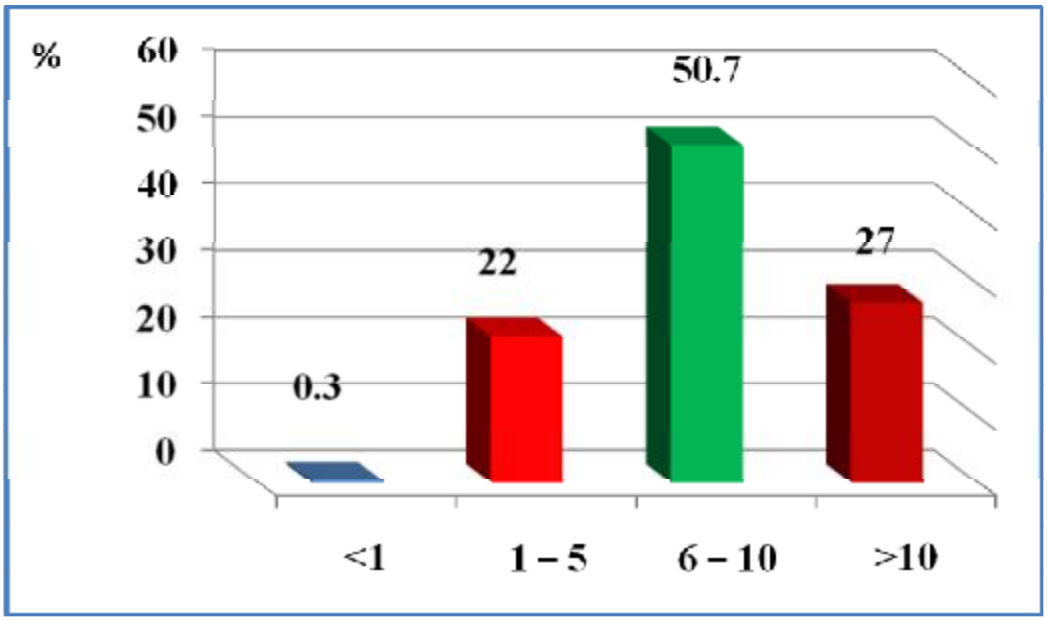

Fig.2:Distribution of the patients according to age.

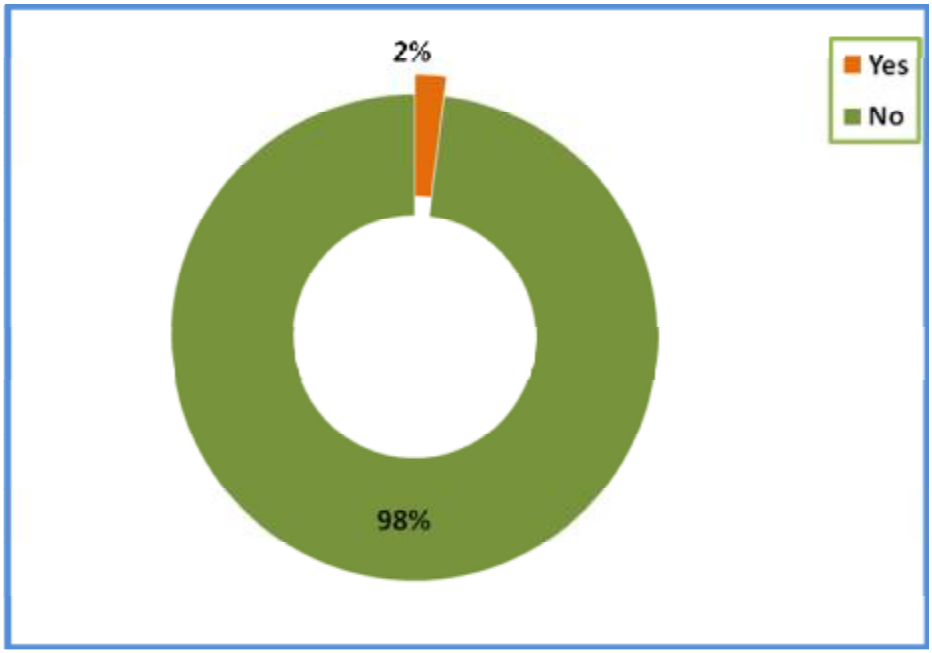

Fig.3:Distribution of the patients according to kobnerization.

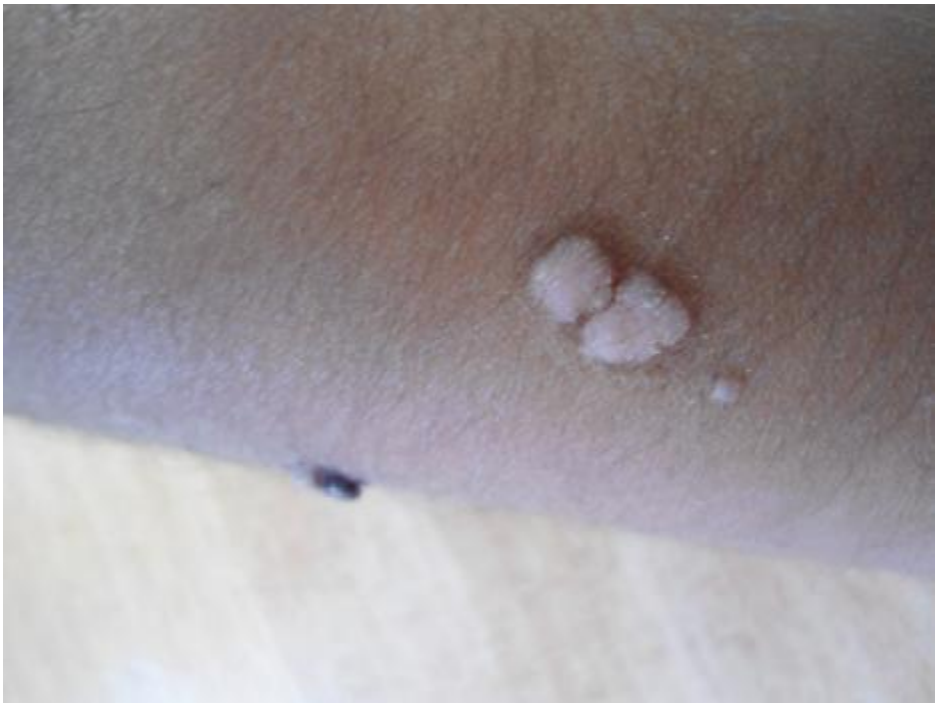

Fig.4: Verruca vulgaris on the arm showing kobner phenomenon.

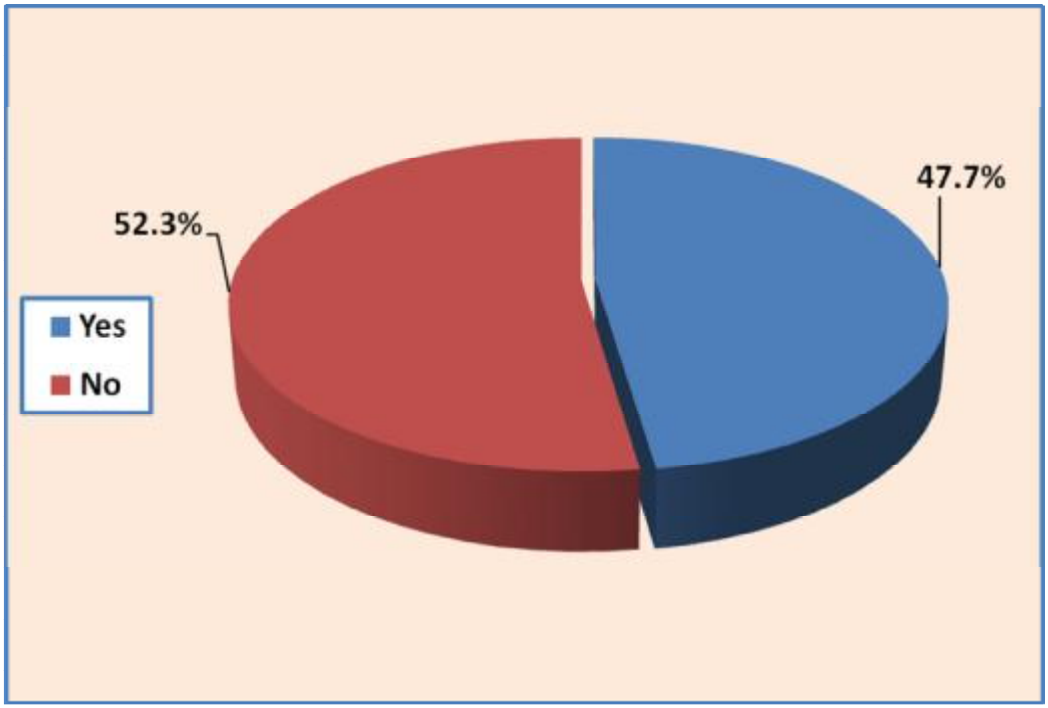

Fig.5 :Distribution of the patients according to family history of the same disease .

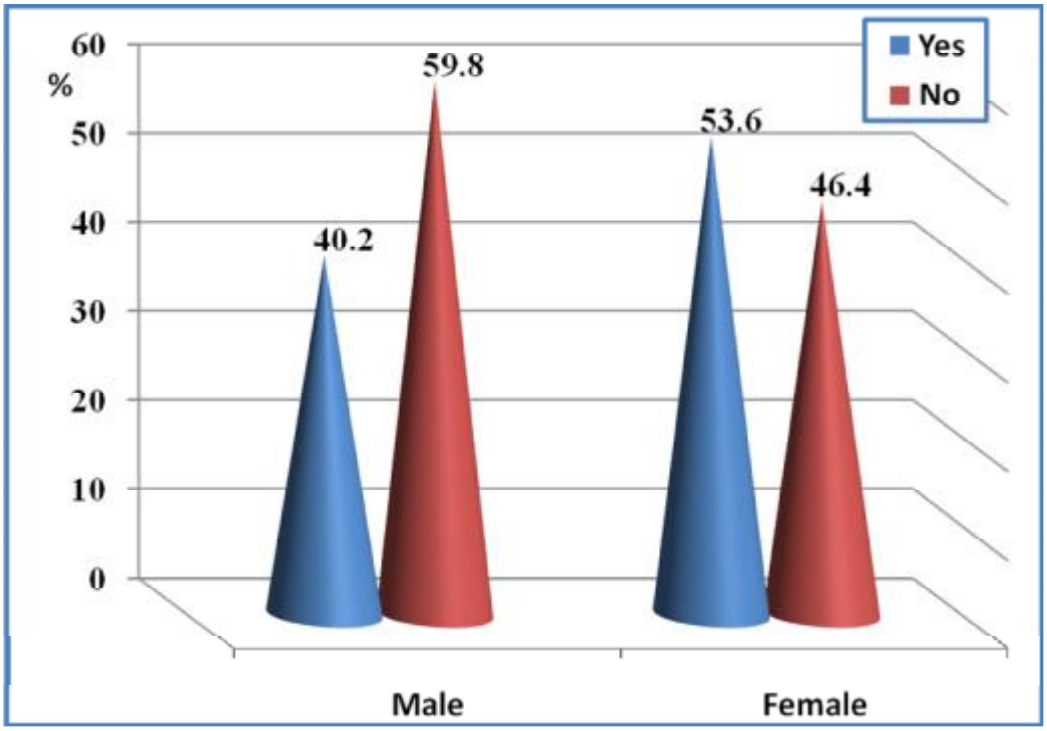

Fig. 6 : Distribution of patients according to family history and sex.

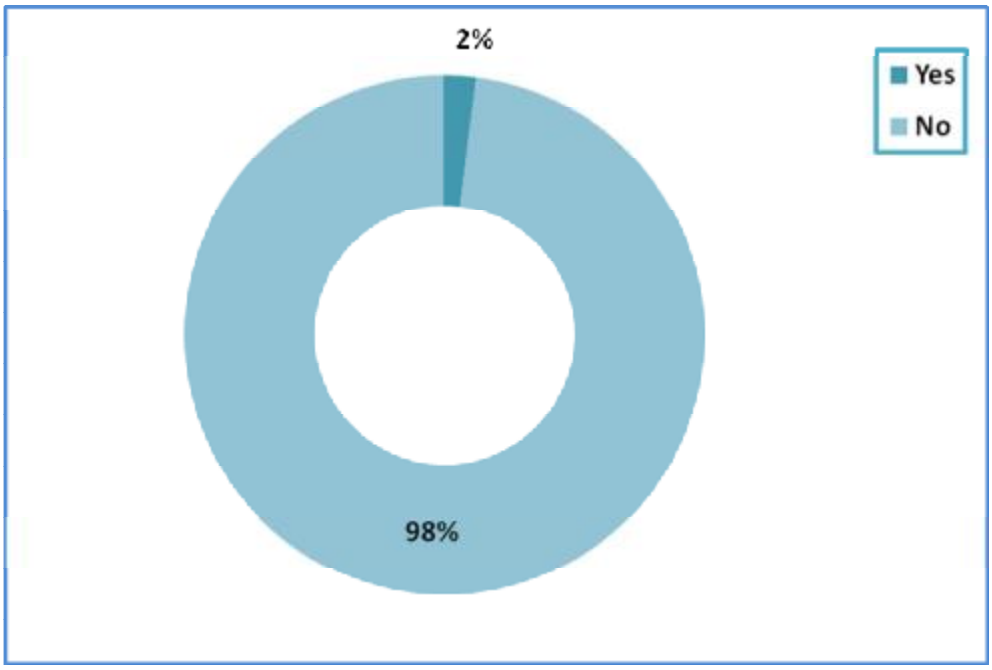

Fig.7:Distribution of the patients according to associated skin diseases .

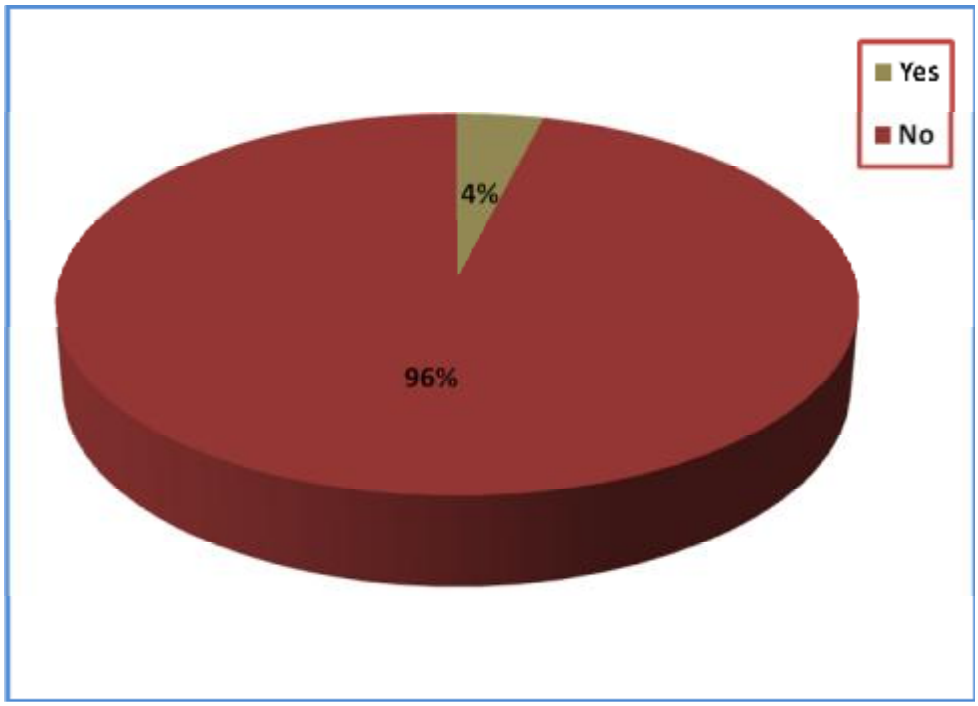

Fig.8a:Distribution of the patients according to associated systemic diseases .

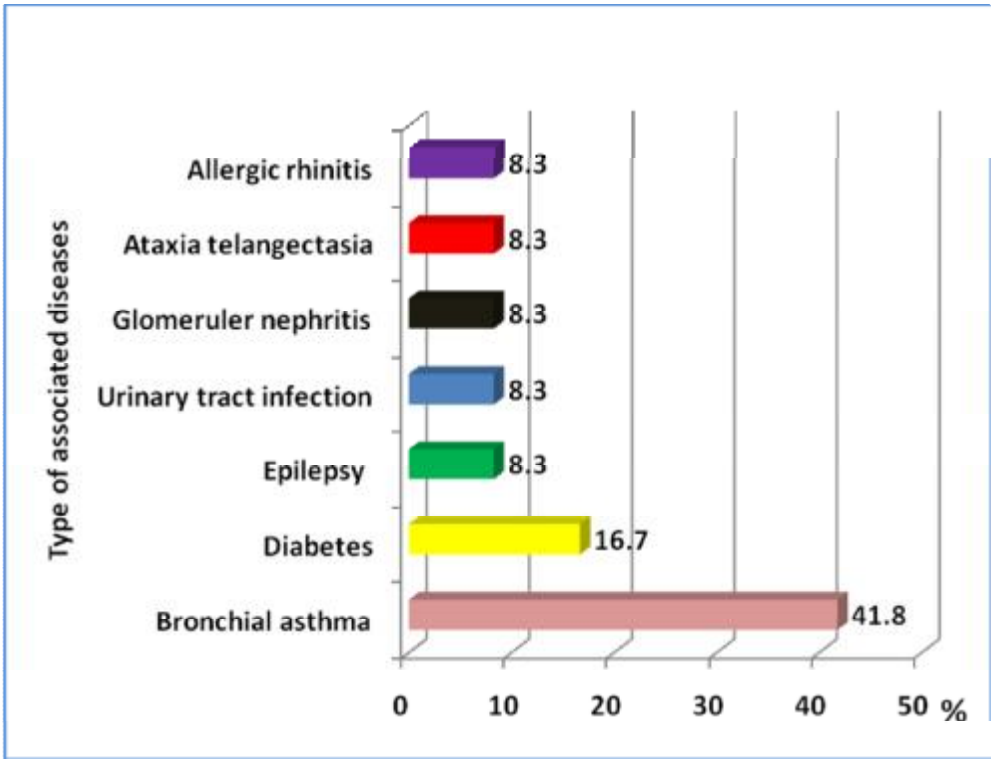

Fig.8b:Distribution of the patients according to type of associated diseases.

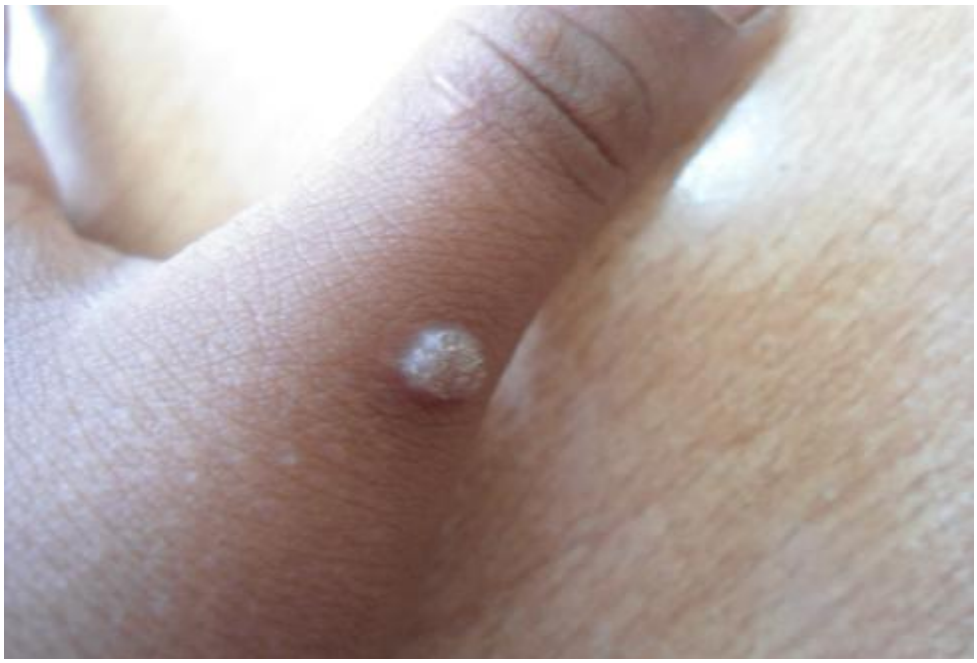

Fig. 9: Verruca vulgaris on the dorsum of left thumb.

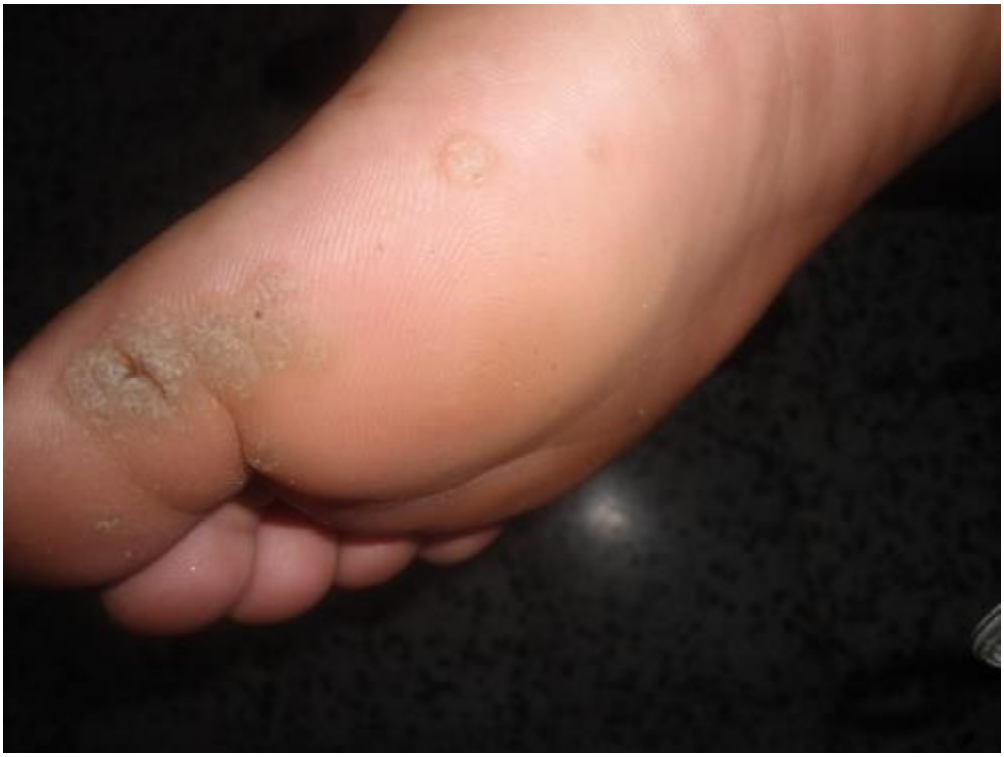

Fig.10: Multiple plantar wart with mosaic pattern.

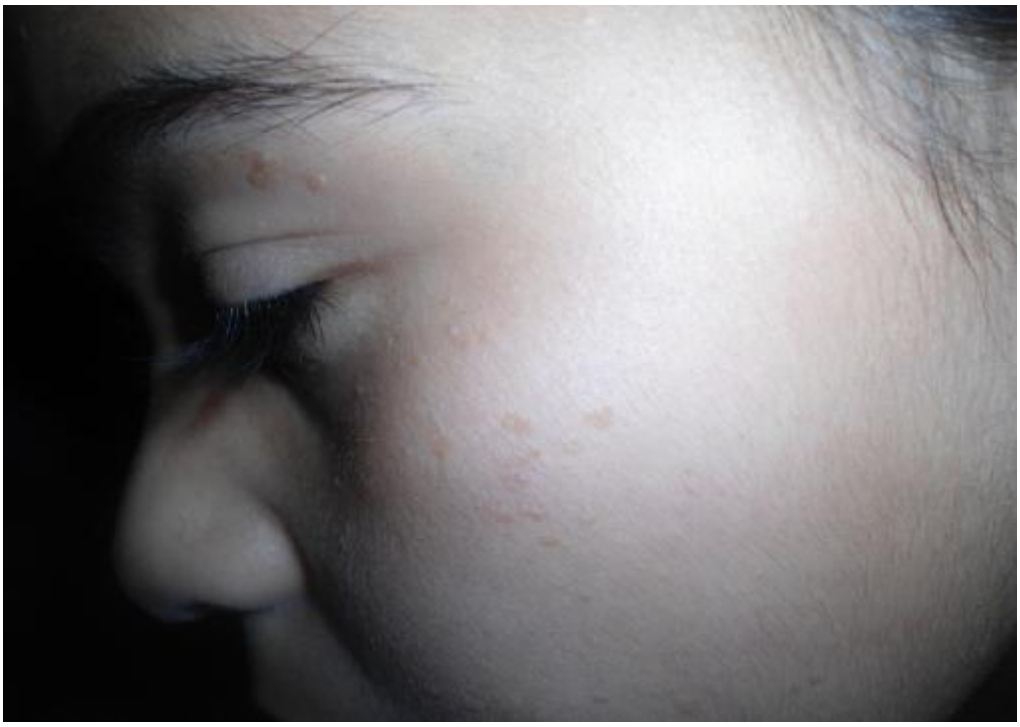

Fig. 11: Verruca plana on the face.

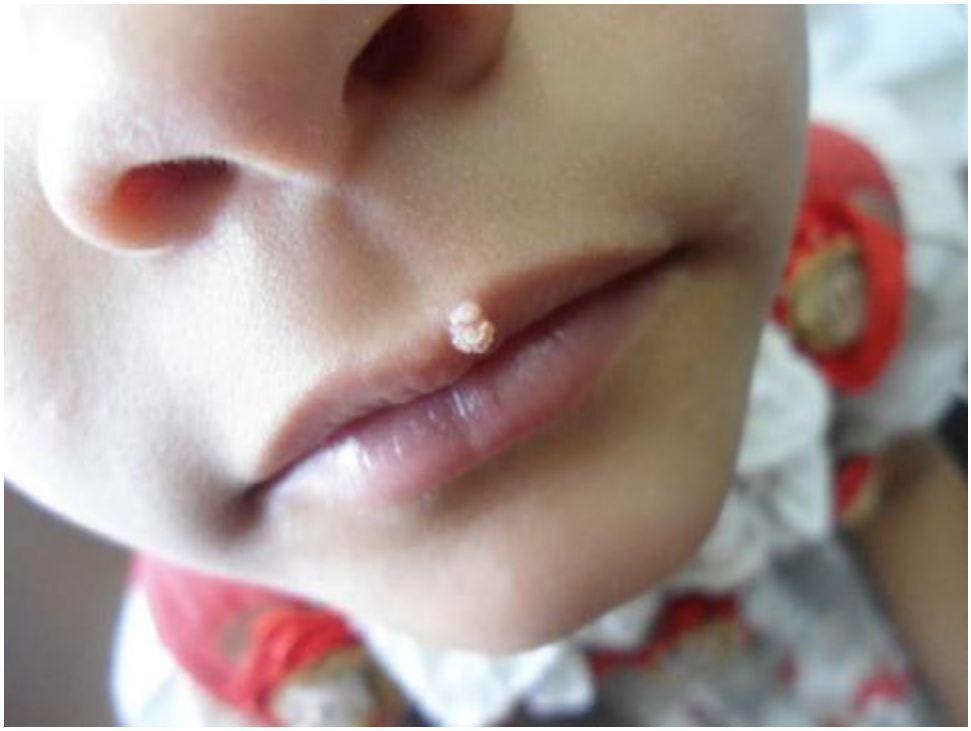

Fig. 12a: Large filliform wart on the upper lip.

Fig. 12b: Large filliform wart on the upper eye lid.

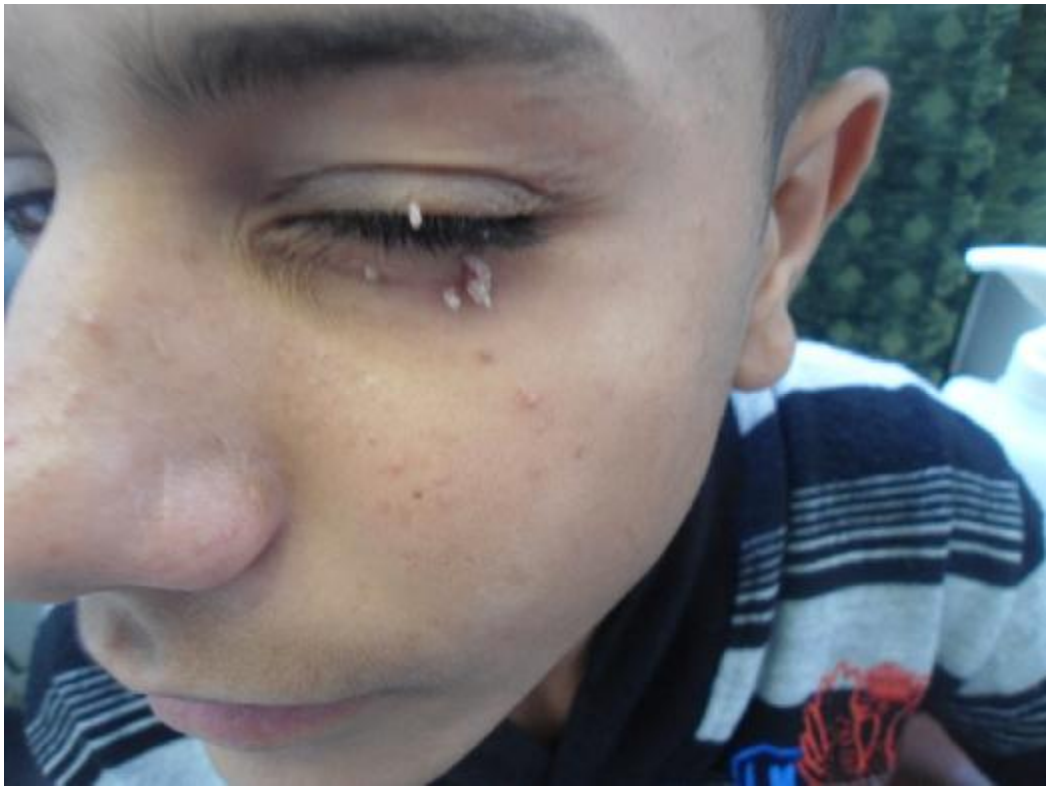

Fig. 12c: multiple filliform wart around left eye.

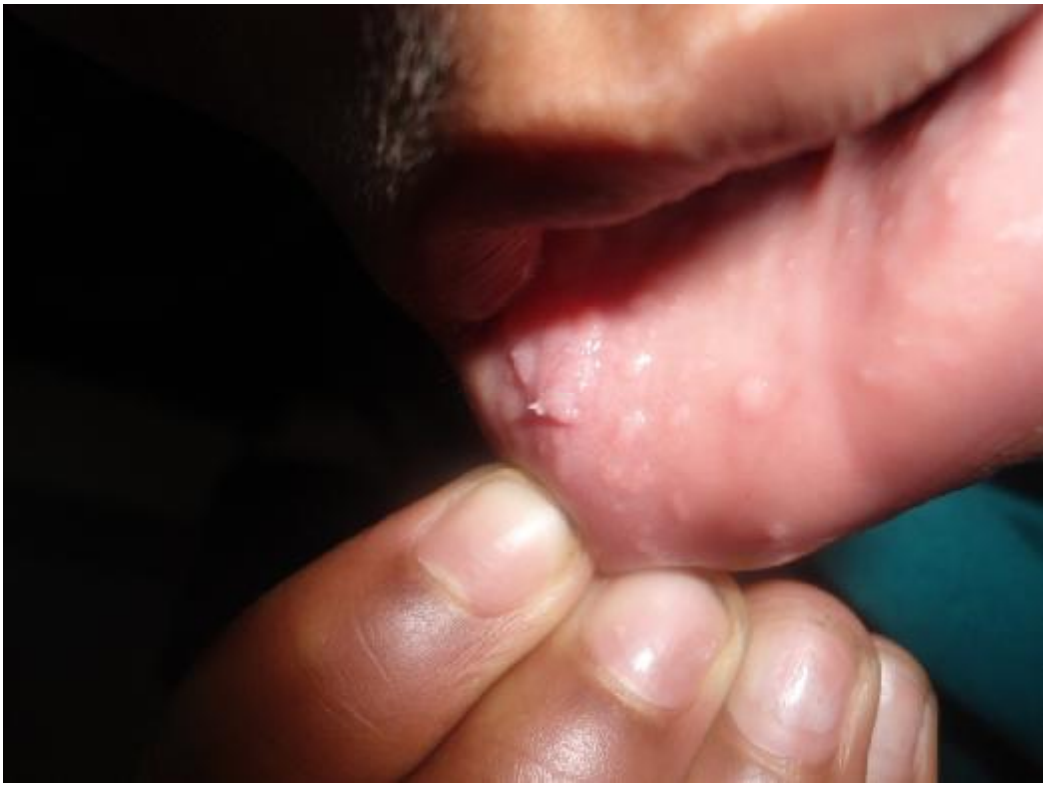

Fig. 13:mucosal wart.

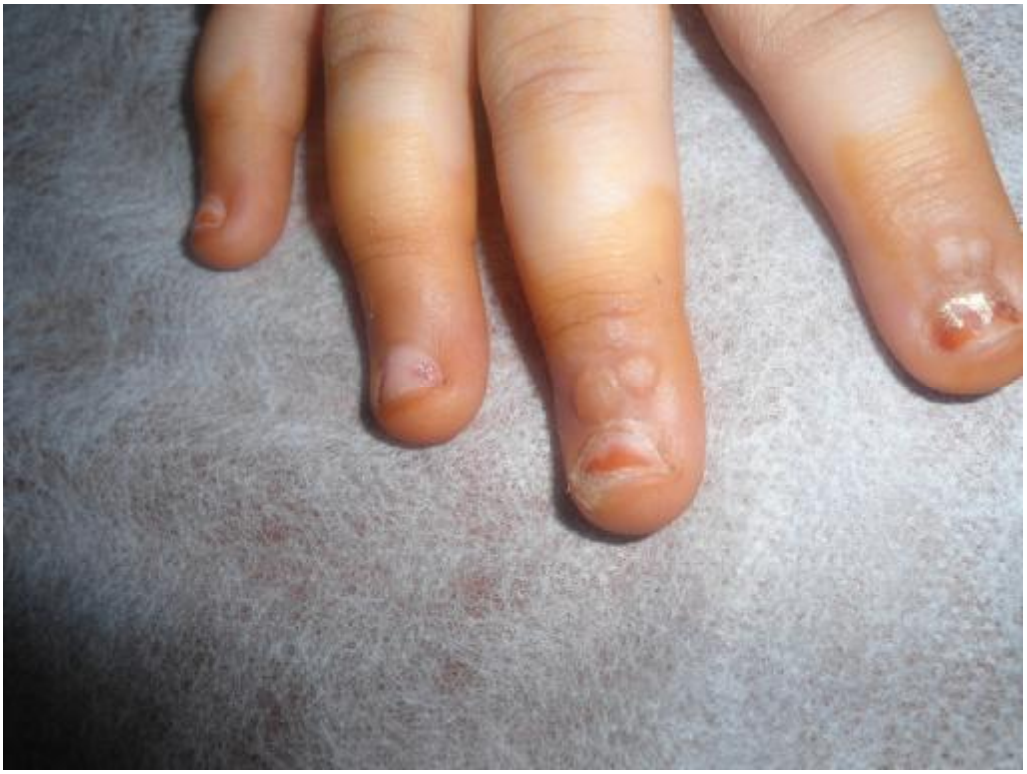

Fig. 14: periungual wart .

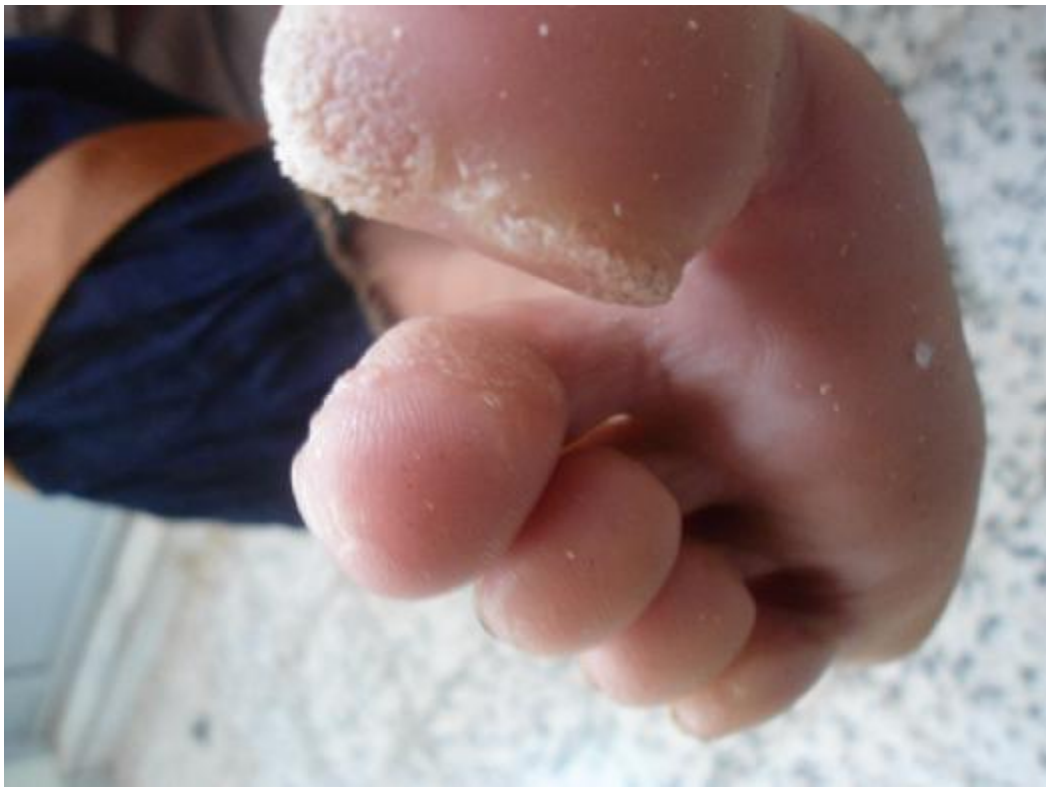

Fig. 15:kissing wart .

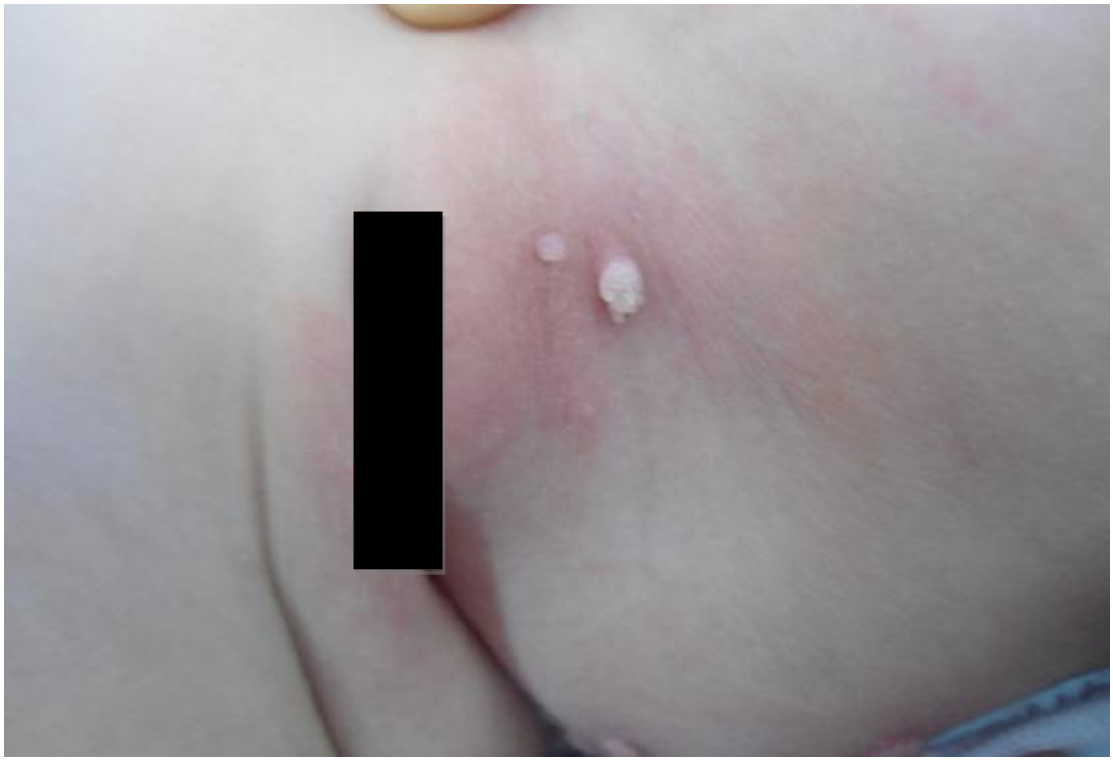

Fig. 16:multiple genital wart.

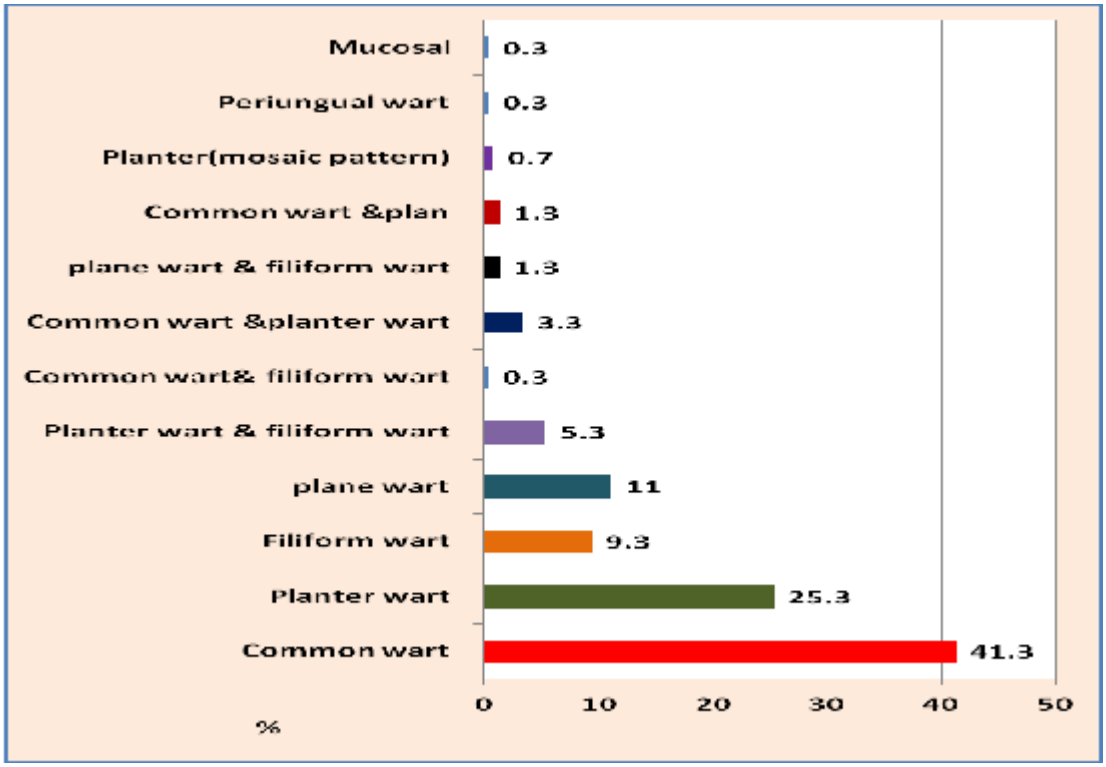

Fig.17:Distribution of the patients according to type of lesion.

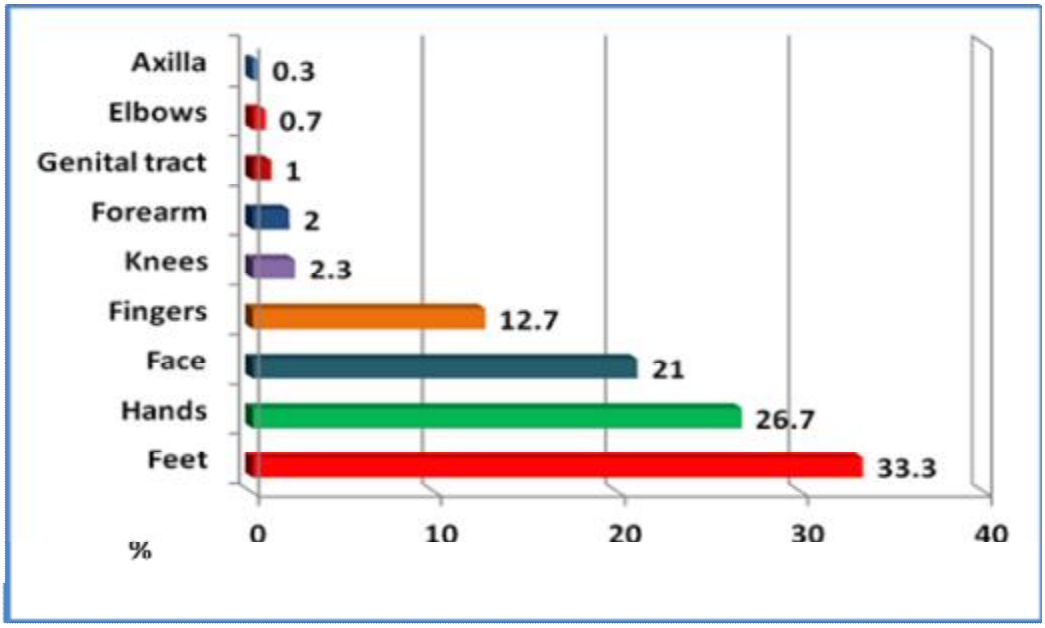

Fig.18:Distribution of the patients according to site of lesion

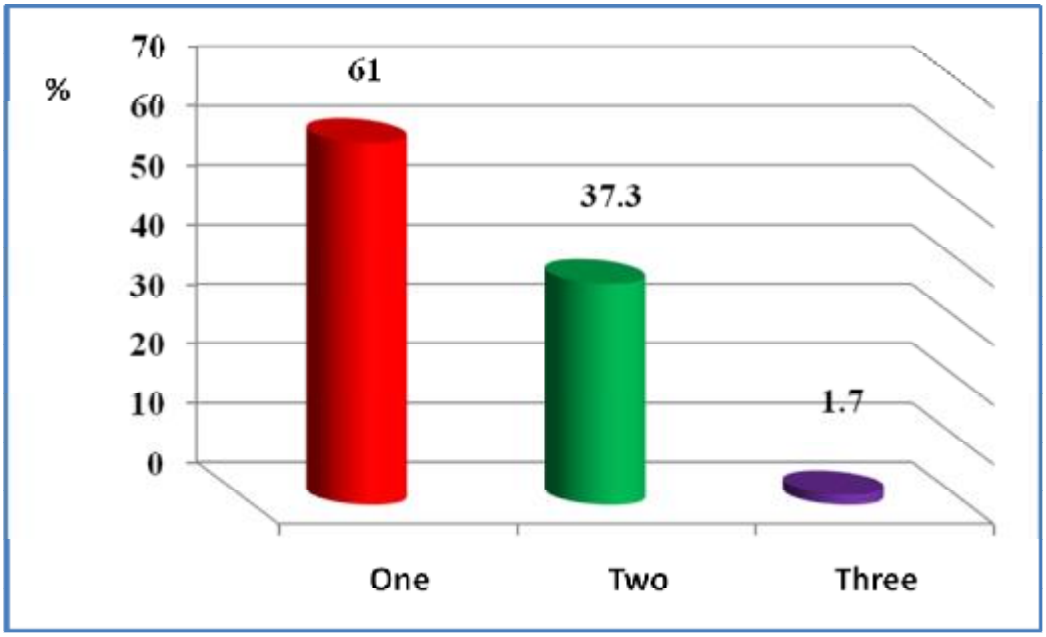

Fig.19:Distribution of the patients according to number of site of lesion.

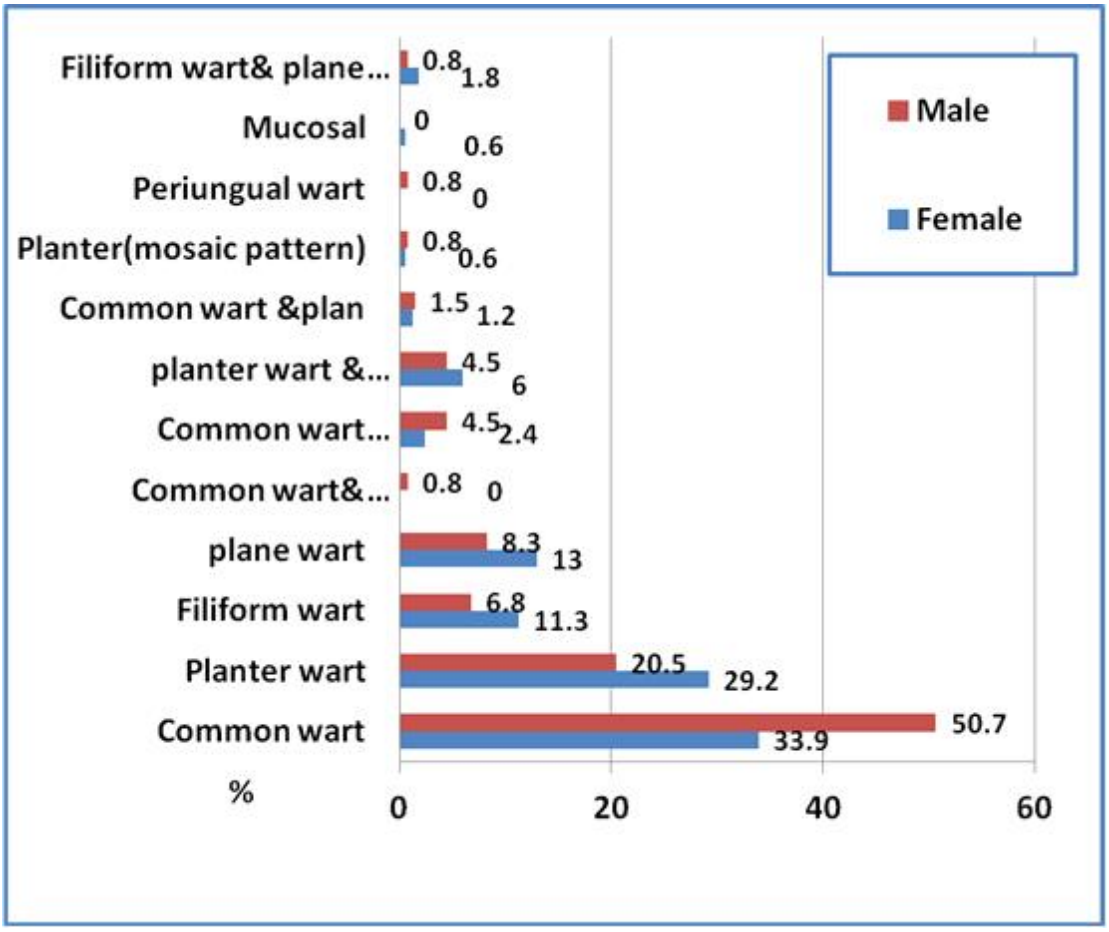

Fig. 20 : Distribution of patients according to type of lesion and sex.

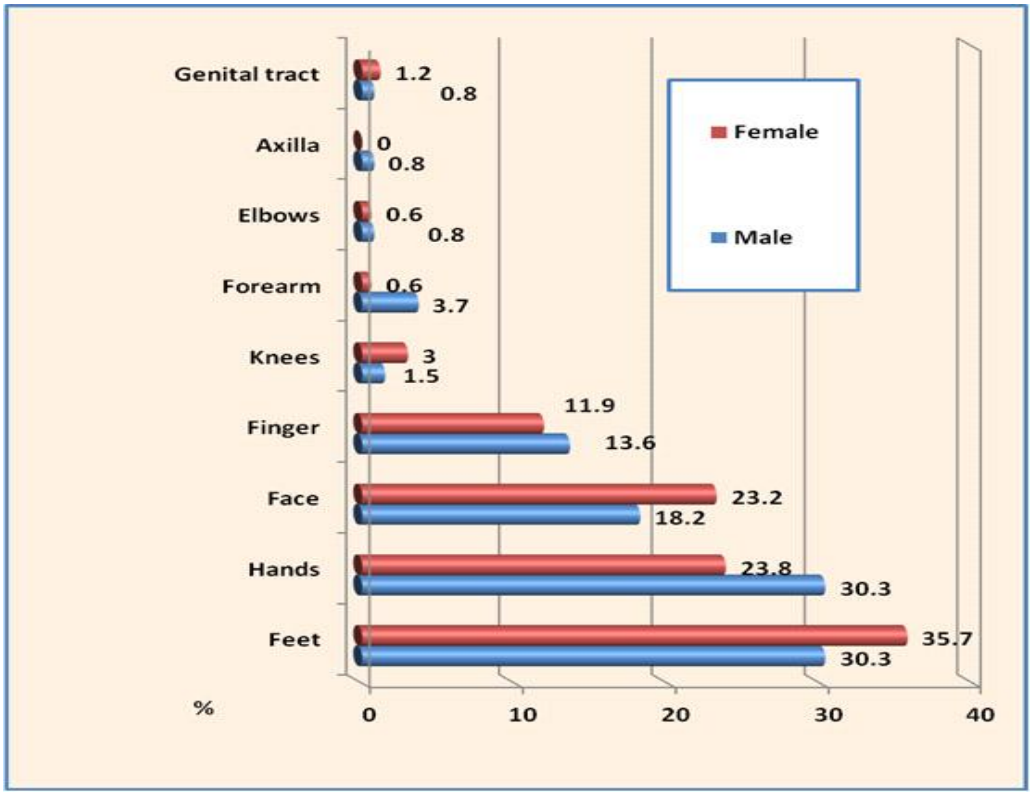

Fig. 21 : Distribution of patients according to site of lesion and sex.

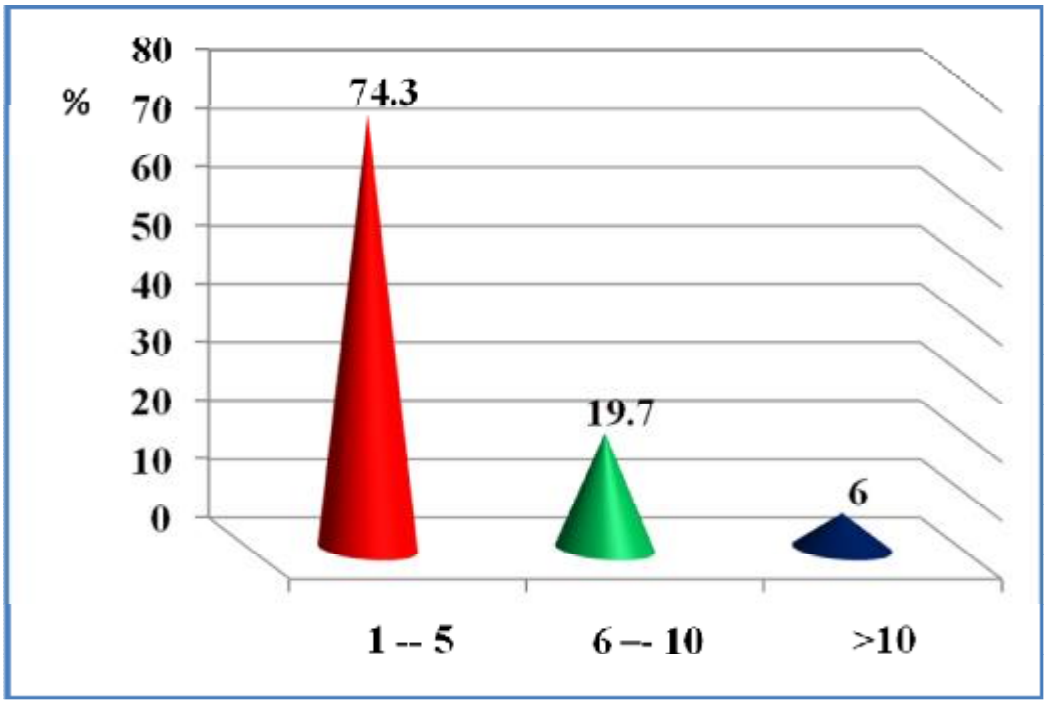

Fig.22 :Distribution of the patients according to number of lesion.

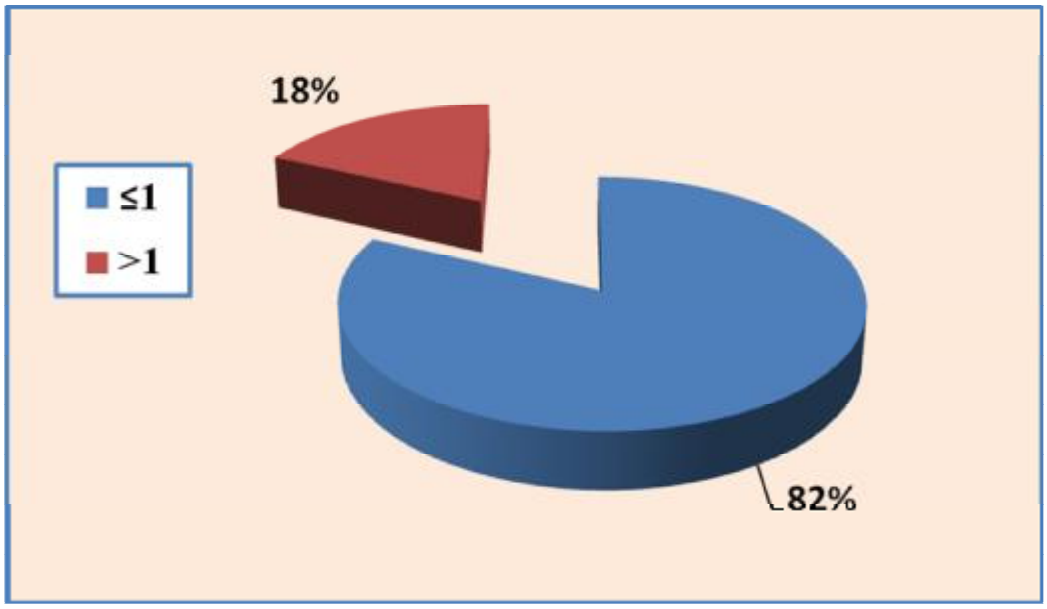

Fig.23 :Distribution of the patients according to duration of the disease.

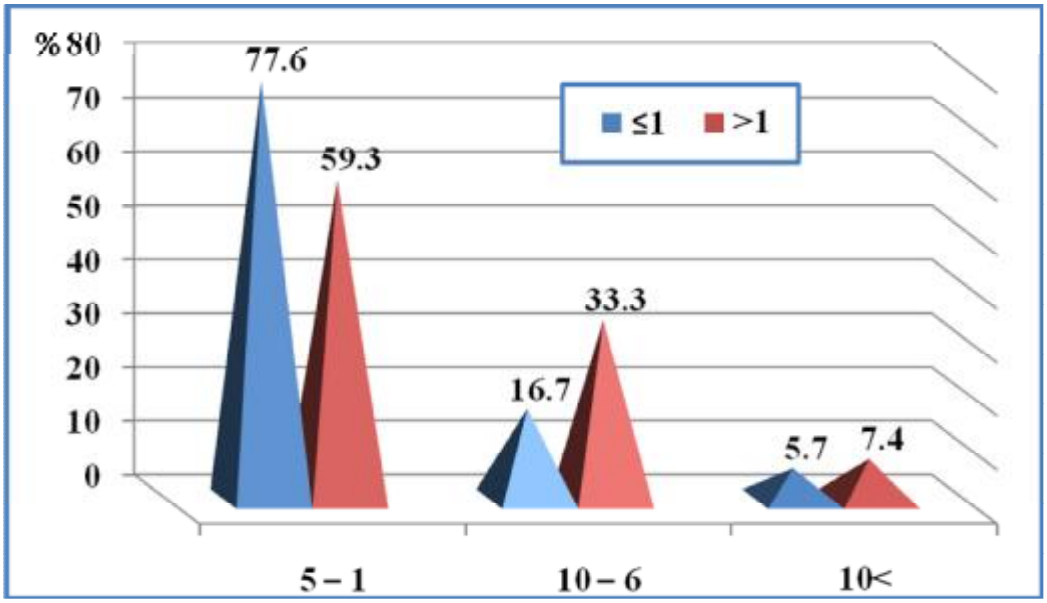

Fig. 24: Distribution of patients according to duration of the disease and number of lesion .

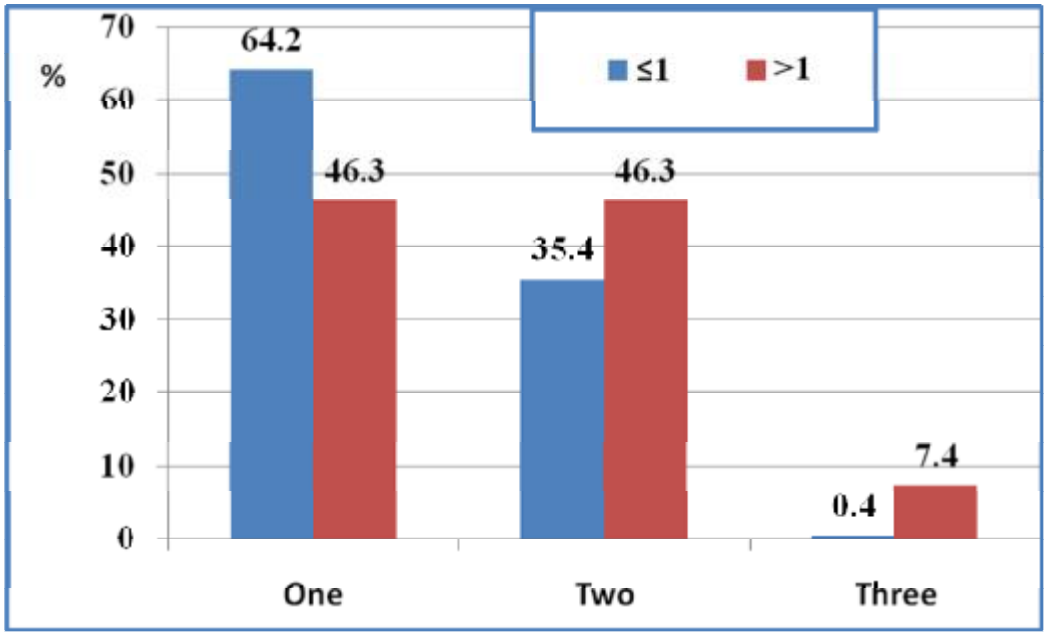

Fig. 25 : Distribution of patients according to duration of the disease and number of site.

Discussion

7-Discussion:

The exact prevalence of warts in the general population is unknown, most people are thought to have been infected at some time in their lives. Infections are spread by contact, either person to person or via some inanimate object. Successful transmission depends on there being a break in the surface of the skin or mucosa so that the virus can gain entery to the basal layers of the epidermis.

Wart occur at any age but are more common in children and adolescents, therefore focus in this study to determine the most common clinical pattern of warts in patients younger than14 years. Although not life threatening, it is common and it causes discomfort to child, anxiety to parents. Warts usually painless, many patients request treatment because of discomfort or social stigma.

In the present study, among 300 child with warts, (56%) were females and (44%) were males, with male to female ratio of 1:1.3, this could be attributed to the fact that females always warries about their shape more than males.

Similarly a study in Kuwait included 2916 children younger than 13 with clinical presentation of warts females were predominate (2).

However, a study in Indian included 90 cases of warts, males, constituted 74.44% of the cases, this high percentage of male, as mentioned in the study could be as result of changing trend of cosmetic interest in males (103).

In the present study mean age of the patients was 8.1 ± 3.2 years, 50.7% of them was in age between 6 and 10 years this could be attributed to the chance of contact were more in this age group, while only 0.3% was less than one year old and 27% was aged more than 10 years. This was in accordance with previous study which reported a mean age 10.24 years (104), moreover, in study from Kuwait reported that the most affected children were between 8 and 10 years (2), and in an Australian study,

the highest prevalence of warts were seen in school- age children (105).

Although kobnerization is a well known phenomenon in warts only (2%) of the patients under study show kobnerization.

Family history of warts were seen in (47.7%) of the patients under study, this was in aggrement with previous study which found an increased risk of the presence of warts in children with a family member with warts (31).

In our study nearly half of patitents had common wart (41.3%), planter wart constitute 25.3%, filiform wart 9.3% , plane wart was constitute 11%.

This result were in aggrement with previous study from India which reported the most common types of warts were common warts 66.6%, followed by planter warts 20.22% , plane warts 7.77% & filiforrm warts 3.33% (103).

Moreover, in hospital clinic in Cambridge reported that 70% of their patients had common warts (17).

Site of lesion were distributed all over the body, in this study (33.3%) of the patients had warts in their feet, while (26.7%) were found in hands, (21 %) were in face, (12.7%) seen in fingers,. therefore patients Seek medical advice because others afraid of shaking their hands and unable to wear sandals.

There is an apparent preference of certain HPV types for either cutaneous or mucocutaneous sites. In the common skin types including HPV(1,2,3, and4) causing warts most frequently on hands, feet and face (106).

However, in other study 9% had hand warts, 20% had plantar warts and 4% had both hand and plantar warts (31).

In the present study lesions localized in one site represent (61%) of the patients, while two sites constitute (37.3%) & three sites were (1.7%).

In this study no statistically significant difference in regard type of wart and site involved between males and females. While in other study, Females were significantly more likely to have plantar warts on their toes and non-plantar warts on their fingers and less likely to have non-plantar warts on the palms of their hands than males (107).

Mean number of lesions were equal to 4.2 ± 3.9, about (74.3%) of the patients were suffering from 1 to 5 lesions, while (19.7%) of the patients had 6 to 10 lesions and (6%) had more than10 lesions.

Mean duration of warts was 9 ± 8.8 months, the minimum duration that was observed one week and maximum duration was 3 years, in this study duration of disease ≤ 1year constitutes to (82%) and >1year (18%) of the patients.

However, in other study the shortest duration was 2 months, while the longest duration was 7 yrs (108).

Moreover, (77.6%) of patient of disease duration ≤ 1year had ≤ 5lesions while (59.3%) of patient of disease duration > 1year had ≤ 5lesions, while (22.4%) of patients of disease duration with ≤ 1year had > 5lesions while (40.7%) of patients of disease > 1year had > 5lesions, this difference was statistically significant p value equal to 0.014.

Noticed the number of warts decreases with prolong duration could be due to develop immunity with time.

Importent to know cell-mediated immunity appears to be the principal mechanism for the rejection of warts. Warts can disappear when the immune response is stimulated. In contrast, in persistent disorders of cell-mediated immunity, the prevalence and severity of warts and the incidence of HPV-related malignancy are increased (17).

However, other study reported that Patients presenting with warts greater than two years in duration were more likely to have multiple warts than those with warts less than one month in duration (31).

Conclusion

8-Conclusion:

- The most common types of warts was common wart.
- The feet being the most frequent site involved.
- Females were more frequently affected.
- They are seen more in school children.
- Family history of wart was positive in 47.7% of the patients.

Recommendation

9-Recommendation:

- Warts are easily spread from person to person ,so transimission can be prevented by avoiding the use of towels and clothes of the infected individual.

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الثآلول هو التهاب جلدي فيروسي شائع يصيب الجلد والأغشية المخاطية أكثر شيوعا في الأطفال والمراهقين لا يسبب الما ولكن يسبب الضيق و الاحراج للمريض وعائلته وينتشر بسرعه كبيره في جسم المريض وبين افراد عائلته .

كان هدفنا من الدراسة تحديد اكثر انماط الثآلول شيوعا في الأطفال والمراهقين اقل من اربعة عشر عام و لربط النو ع مع العمر والجنس و اكثر الاما كن اصابه في جسم المريض وحجم الاصابة و عدد ومدة الآفة ونسبة انتقال الثآلول بين افراد العائلة.

تم جمع ثلاثمائة مريض من المترددين على العيادة الخارجية وعيادة الكي بمستشفى الجمهورية الذين تقل أعمارهم عن اربعة عشر عاما خلال ستة شهور إبتداءاً من مارس 2012.

اخدت جميع المعلومات اللازمة كما تم فحص الجلد فحص دقيق لتحديد نوع الثآلول وعدده ومكان الإصابة.

تم تحليل البيانات التي تم جمعها إحصائيا باستخدام برنامج حاسوب و اختبار كاي تربيع وبمستوي معنوية مؤثرة (P)=0.05 .

اظهرت نتائج الدراسة ان الثآلول الـ شائع هو اكثر انواع شيوعا(41.3%) عند الفئة العمريه اقل من اربعة ع شر عاما يتبعه الثآلول القدمي (25.3%) ويليه الثآلول الخيطانى(9.3%) , وكان نسبة الذكور إلي الإناث 1 : 1.3, معظمهم في سن ما بين 6 و 10 سنوات (50.3 %) , و وجد ان نسبه انتقال الثألول في العائله47.4 % ٍ وكان نسبة انتقال الإصابة أكثر حدوثاً مع المرضى الإناث , كما لو حظ ان الثألول تـ مركز ظهوره في القدمين بنسبة 33 % واليدين بنسبة 26.7 % , ولكن لا يوجد اختلاف ما بين الذكور والأناث في عدد واماكن توجد الثألول , و ان عدد الثألول الذي يقل عدده من 5 أكثر حدوثاً بنسبة (74.3%) .

وكانت اكبر فترة زمنية للثألول سجلت في هذه الدراسة 3 سنوات وأقل فترة زمنية سجلت اسبوع كما اظهرت نتائج الدراسة ان الثألول يتناقص عدده مع طول فترة الإصابة وهذا يرجع إلي تطور مناعة المريض .