INTRODUCTION

Warts are benign epithelial proliferations induced by several types of human papilloma virus (HPV). Viral warts are one of the most common skin diseases, which can range in severity from a minor nuisance that resolve spontaneously to a troublesome, chronic condition ***(Wimmersdrof et al., 2008).***

Warts still represent a therapeutic challenge. Many treatments have been used, but no single optimal treatment has been determined ***(Kwok et al., 2012).***

Common therapeutic modalities include cryotherapy, keratolytics, topical immunotherapy with contact sensitizer, oral cimetidine, antimitotic agents, carbon dioxide laser, electrosurgery, topical immune response modifier, photodynamic therapy and intralesional injection of antigens ***(Park and Choi, 2008).***

Warts that fail to respond to conventional treatment are considered to be recalcitrant ***(Berth-Jones and Hutchinson, 1992).*** Recalcitrant warts remain a challenging problem to treat, with considerable morbidity for patients ***(Oni and Mahaffey, 2011)***. ***Berth-Jones and Hutchinson 1992*** attained a cure rate of only a maximum of 52% by treating recalcitrant warts using a combination of cryotherapy and topical paints. Later on, several researchers have discussed the effectiveness of Pulsed

Dye Laser (PDL) treatment for use in recalcitrant verrucae therapy ***(Kenton and Tan, 1999; Schellhaas et al., 2008; Sethuraman et al., 2010; Kowk et al., 2012).***

The mechanism of action of PDL treatment for warts is based on the specific destruction of the superficial dilated capillaries in warts by selective photothermolysis of oxyhemoglobin within the microvasculature. The wavelength of the PDL is found in the yellow light spectrum (595 nm), which is absorbed from hemoglobin and oxyhemoglobin. The damage of virally-infected keratinocytes by PDL may also contribute to the treatment for warts because HPV is heat-sensitive ***(Vargas et al., 2002).***

AIM OF THE WORK

The aim of this study is to assess the efficacy of 595 nm PDL in treatment of recalcitrant plantar warts as regards the clinical response, number of sessions, side effects, and feasibility.

WARTS

Warts are benign proliferations of skin and mucosa caused by HPV. Certain HPV types tend to occur at particular anatomic sites, however warts of any HPV type may occur at any site. The primary clinical manifestations of HPV infection include common warts, genital warts, flat warts, and deep palmoplantar warts (myrmecia). Less common manifestations of HPV infection include focal epithelial hyperplasia (Heck's disease) ***(Cohen et al., 1993).***The treatment of warts posses a therapeutic challenge for physicians. No single therapy has been proven effective in achieving complete remission for every patient. As a result, many different approaches to wart therapy exist ***(Bacelieri and Johnson, 2005).***

History of Warts

Cutaneous warts (verrucae) were known to the ancient Greeks and Romans in the 1st century AD. Until the 20th century, genital warts were believed to be a form of syphilis or gonorrhea. In **1907**, the Italian physician **Giuseppe Ciuffo** established the viral etiology for human warts. In 1949, the viral particle was observed using an electron microscope. Since 1976, more than 100 types have been isolated and identified based on polymerase chain reaction (PCR) amplification products. Distinctions between HPV types include the type of epithelium typically infected (cutaneous or genital/mucosal)

and the most serious anticipated outcome (benign proliferation or malignancy) ***(Nebesio et al., 2001).***

Human Papilloma Virus

Papilloma viruses (from the Latin papilla, 'nipple or pustule' and the Greek suffix-oma, which is 'tumour') are members of the Papovaviridae family ***(Zheng and Baker, 2006).***

Human papilloma virus virion is 55 nm in diameter which causes cutaneous viral warts, most commonly located on the skin and genitalia. HPV are highly specific and do not infect other species, even under laboratory conditions where humans are the only known reservoir for HPV. The HPV is characterized by a capsid lacking an envelope, rendering HPV very stable, infectious for years, and resistant to many therapeutic agents ***(Rivera and Tyring, 2004).***

Human papilloma virus is composed of a double-stranded (ds) circular DNA with approximately 8000 base pairs, which encode eight gene proteins: E ("early", six genes,) and L ("late", two genes, L1, L2). The E genes interfere with cell cycle regulation, which is related to tumour formation/malignant phenotypes, genome replication/ expression, and release of the virus. The L genes encode the proteins forming the capsid. HPVs are epitheliotrophic and host-specific, each infecting only

its natural host. HPVs do not infect laboratory animals and do not propagate in tissue culture ***(Brown et al., 1999).***

HPV Lifecycle

The viral replication cycle appears to be linked to epithelial differentiation and keratinocyte maturation. Figure (1) illustrates HPV lifecycle ***(Frazer, 2004).*** Infection typically occurs when basal cells in the host are exposed to infectious virus through a disturbed epithelial barrier as would occur during sexual intercourse or after minor skin abrasions **(*Sanclemente and Gill, 2002).***

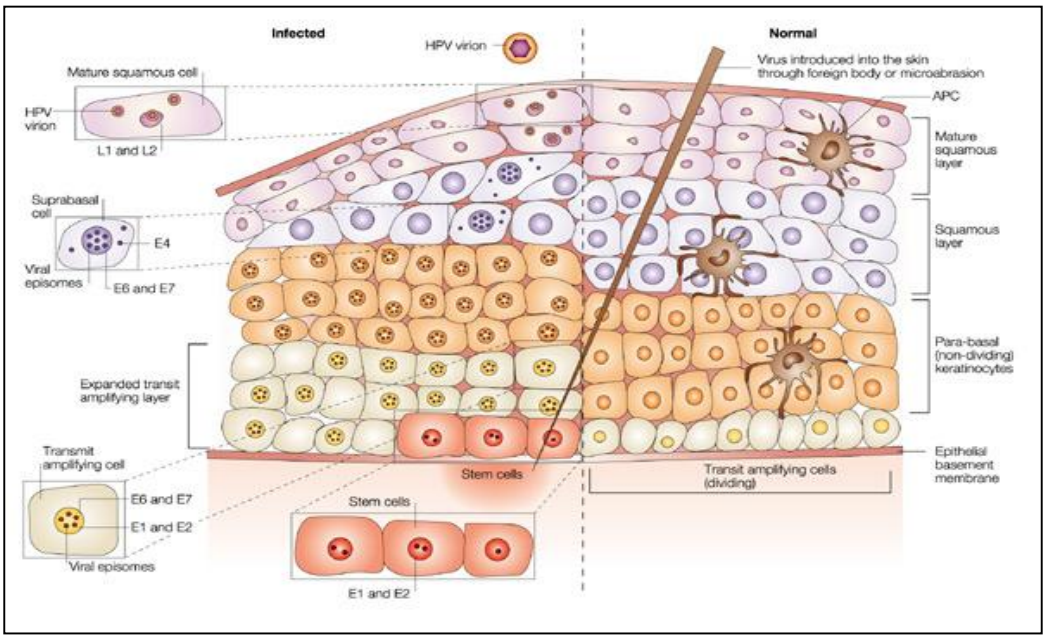

Figure (1): Papilloma virus lifecycle ***(Frazer, 2004).***

To establish infection, the virus must infect basal epithelial cells that are long lived or have stem cell–like properties. Microtrauma to the suprabasal epidermal cells probably enables the virus to infect the cell within the basal layer. The viral genome maintains itself as an episome in basal cells, where the viral genes are poorly expressed. Viral replication takes place in suprabasal layers and is tied to the epidermal differentiation process. The presence of the virus causes morphological abnormalities in the epithelium, including papillomatosis, parakeratosis, and koilocytosis. Progeny virus is released in desquamated cells. HPV infections have not been shown to be cytolytic, rather viral particles are released as a result of degeneration of desquamating cells. The HPV can survive for many months and at low temperatures without a host; therefore, an individual with plantar warts can spread the virus by walking barefoot ***(Sanclemente and Gill, 2002).***

Histopathology of Warts

Histologically, a wart demonstrates acanthotic epidermis with papillomatosis, hyperkeratosis and parakeratosis with elongated rete ridges often curving towards the center of the wart. Dermal capillary vessels are prominent and may be thrombosed, and mononuclear cells may be present. HPV-associated papillomas are characterized by large keratinocytes

with an eccentric, pyknotic nucleus surrounded by a perinuclear halo (koilocytes) by electron microscope. HPV infected cells may have small eosinophilic granules and diffuse clumps of basophilic keratohyaline granules and are not HPV particles.

Flat warts have less acanthosis and hyperkeratosis and do not contain parakeratosis or papillomatosis, but they do have abundant koilocytes. Anogenital warts may express slight to extensive acanthosis and parakeratosis since they are within or adjacent to a mucosal surface and do not have a granular layer. Koilocytes are often observed in anogenital warts, and the rete ridges often form thick bands extending extensively into the underlying, highly vascular dermis ***(Lowry and Androphy, 2003).***

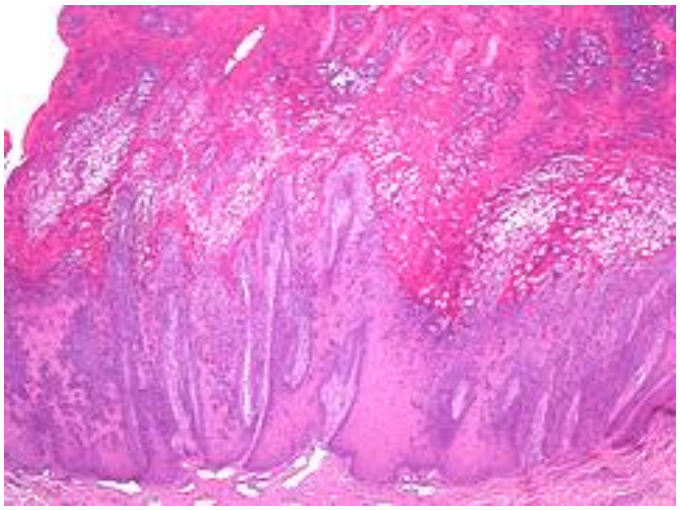

Figure (2): Verucca plantaris (H&E) (x100) ***(Kimura et al., 2006).***

As regard plantar warts, they showed considerable elongation of dermal papillae with corresponding rete ridges which incline inwards at the base and gives rise to a cauliflower appearance. This lies beneath the surface and is usually covered with thick horney cap with surrounding ring of hyperkeratosis, with symmetric and endophytic lesions characterized by epidermal hyperplasia and presence of large intracytoplasmic, keratohyaline granules in the superficial keratinocytes ***(Lowry and Androphy, 2003).*** Figure (2) illustrates plantar wart under light microscope (H&E) with magnification (x100) ***(Kimura et al., 2006).***

Classification of Warts

Human papilloma viruses produce epithelial tumours of the skin and mucous membranes. More than 100 HPV types have been detected, and the genomes have been completely sequenced. HPVs are involved in many diseases. Table (1) summarizes these different diseases and the responsible HPV types. The classification system, which is based on similarities in their genomic sequences, generally correlates with the 3 categories used to describe HPV clinically: nongenital cutaneous, nongenital mucosal and anogenital diseases ***(Gearhart, 2006).***

Table (1): Diseases and associated HPV subtypes ***(Gearhart, 2006).***

Diseases	HPV subtype
Nongenital Cutaneous Disease	
Common warts (verrucae vulgaris)	1, 2, 4, 26, 27, 29, 41, 57, 65
Plantar warts (myrmecias)	1, 2, 4, 63
Flat warts (verrucae plana)	3, 10, 27, 28, 38, 41, 49
Butcher's warts	1, 2, 3, 4, 7, 10, 28
Mosaic warts	2, 27, 57
Ungual squamous cell carcinoma	16
Epidermodysplasia verruciformis	5, 8, 9, 10, 14, 17, 20, 21, 22, 23, 24, 25, 37, 38
Nongenital Mucosal Disease	
Respiratory papillomatosis, Oral florid papillomatosis (Ackerman tumour)	6, 11
Squamous cell carcinoma of the lung	6, 11, 16, 18
Laryngeal papilloma	6, 11, 30
Laryngeal carcinoma	16, 18
Maxillary sinus papilloma	57
Squamous cell carcinoma of the sinuses	16, 18
Conjunctival carcinoma	16
Oral focal epithelial hyperplasia (Heck's disease)	13, 32
Oral carcinoma, Oral leukoplakia	16, 18
Anogenital Disease	
Condyloma accuminatum	6, 11, 30, 42, 43, 44, 45, 51, 52
Bowenoid papulosis	16, 18, 34, 39, 42, 45
Bowen's disease	16, 18, 31, 34
Buschke-Löwenstein tumours	6, 11
Intraepithelial neoplasia	30, 34, 39, 40, 53, 57, 59, 61, 62, 64, 66, 67, 68, 69
Carcinoma of vulva	6, 11, 16, 18
Carcinoma of vagina & cervix	16, 18, 31
Carcinoma of penis	16, 18

Plantar verrucae in HIV-positive patients may be associated with unusual HPV types and should be analyzed and treated aggressively given the potential for a more distinct clinical manifestation. Identification of HPV-69, an HPV type previously reported to be rare and associated with dysplastic lesions, was confirmed by HPV DNA dot-blot hybridization with specific DNA probes for each known HPV type in a clinically aggressive plantar verruca from an HIV-positive patient ***(Whitaker et al., 2009).***

Clinical Types of HPV

1. Cutaneous forms

Common warts

They are hyperkeratotic, exophytic and dome-shaped papules or nodules mostly associated with HPV-1, 2 or 4. They are most commonly located on fingers, the dorsal surfaces of hands and other sites prone to trauma such as knees or elbows, but may occur at any anatomical location. Autoinoculation by scratching may cause a linear arrangement of warts. Involvement of the nail fold (eponychium) may also occur ***(Kirnbauer et al., 2003).***

Palmar and plantar warts

Palmar warts appear as thick, endophytic papules on the palms and lateral aspects of the hands. On the sole, plantar

warts are hyperkeratotic lesions on the plantar surface, they tend to develop over areas of pressure such as the heel. Plantar warts that coalesce into large plaques are referred to as mosaic warts ***(Egawa, 1994).*** They are often endophytic (i.e. they grow into the deeper layers of skin because of pressure). Although they are generally self-limited, plantar warts should be treated to lessen symptomatology, decrease duration and reduce transmission ***(Landsman et al., 1996).***

As regard deep palmoplantar warts also termed myrmecia, they begin as small shiny papules, sharply defined, round lesions with a rough keratotic surface, and surrounded by a smooth collar of calloused skin. Myrmecia warts that occur on the plantar surface are usually found on weight-bearing areas, such as the metatarsal head and heel. When they occur on the hand, they tend to be subungual or periungual ***(Philip and Shenefelt, 2009).***

Plantar warts are caused by HPV usually of type 1, 2 or 4. The virus attacks the epidermal layers through direct contact especially if there are breaks in the stratum corneum ***(Johnson, 1995).***

Autoinoculation of the virus into opposed lesions is common. The HPV can survive for many months and at low temperatures without a host therefore an individual with plantar warts can spread the virus by walking barefoot. Clinically detectable verrucae develop from a few weeks to 18 months after inoculation. In most infected individuals, the virus is

carried subclinically and never produces apparent lesions ***(Nebesio et al., 2001).***

Plantar warts may cause pain particularly when walking. They may also cause leg or back pain secondary to distortion of posture. They may spread to other sites, but not to histologically dissimilar areas (i.e plantar warts do not spread to genitalia).

Callosities are another name for callus, which are thickening of the skin due to intermittent pressure and frictional forces resulting in hyperkeratosis ***(Coughlin, 2000).***They differ from warts by the central pinpoint petichae or punctuate black dots which represent thrombosed capillaries and capillary bleeding that follows shaving of the hyperkeratotic surface of the wart ***(Kirnbauer et al., 2003).***Moreover, warts are painful on application of pressure from either side of the lesion rather than direct pressure; unlike calluses which tend to be painful on direct pressure instead ***(Gearhart et al., 2011).*** Callosities are always found in weight bearing area where neither skin line deviation nor vascular changes can be detected through callous ***(Van Brederode and Engel, 2001).***

Flat warts (*verrucae planae)*

Flat warts (verrucae planae) are smooth, flat-topped variants of common warts that are 2 to 4 mm in diameter. They most often occur on the face and extremities of children and on the lower legs of women, where they may spread by shaving ***(Stulberg and Hutchinson, 2003).*** They are usually caused by

HPV types 3 or 10 and less often by 27 and 28 ***(Kirnbauer et al., 2003)*.**

Butcher's warts

These earn their name from their occurrence in meat processing professionals. They appear as extensive verrucous papules or cauliflower-like lesions on the dorsal, palmar or periungual aspects of the hands and fingers and are mostly associated with HPV 7. They are not caused by animal papillomavirus types ***(Keefe et al., 1994).***

Epidermodysplasia verruciformis (EDV)

Epidermodysplasia verruciformis (EDV) is an inherited disorder in which there is a mild defect of cell-mediated immunity and widespread and persistent infection with HPV. The lesions vary considerably and may be flat, wart-like lesions, often pigmented, red or atrophic macules and branny pityriasis versicolor-like plaques. The flat, wart-like lesions are frequently localized to the extremities and the face and thicker plaques may resemble seborrhoeic keratoses. EDV-specific HPV types include HPVs 5,8,9,14,17,25, and 38, but mainly types 5 and 8 are detected in EDV-associated skin cancers. There is a risk of development of squamous cell carcinoma on sun-exposed skin ***(Sterling et al., 2001).***

2. Mucosal forms

More than 25 HPV types infect the mucosa of the anogenital, the upper respiratory and the digestive tracts. Subclinical infections are much more common than visible warts. Application of 5% acetic acid (aceto-whitening) may aid in the identification of subclinical lesions as white areas ***(Kirnbauer et al., 2003; Verma and Khanna, 2012)***.

Condylomata acuminatum

Condylomata acuminatum classically are soft, fleshy, and vascular. They usually appear on moist surfaces, such as the vaginal introitus, preputial sac, or perianal area. These lesions typically have a distinct clinical appearance marked by a raised, granular surface, often with multiple small finger like projections. With magnification, a central venule can be seen within each projection. Multiple and coalescing lesions are common ***(Oriel, 1990)***.

Other types of anogenital warts have been described: (1) Keratotic genital warts have a thickened, horny surface. They resemble common skin warts and are most often found on dry surfaces. (2) Smooth papular wart, an exophytic lesion without the cauliflower appearance of condylomata acuminata .These are usually found in relatively dry locations, such as the shaft of the