Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet
on
Giant Condyloma Acuminatum

Introduction

Giant condyloma acuminatum**,** also known as a Buschke–Löwenstein tumour and 'Giant condyloma of Buschke–Löwenstein tumour' is a rare cutaneous condition characterised by an aggressive, wart-like or cauliflower-like growth that is a verrucous carcinoma (an uncommon variant of squamous cell carcinoma). It is attributed to human papillomavirus infection.

[Picture Credit: Female Condylomata Acuminatum]

It was first described by Buschke and Löwenstein in 1925. The giant condyloma of Buschke and Löwenstein (GCBL) is a slow-growing, locally destructive verrucous plaque that typically appears on the penis and vulva, but may occur elsewhere in the anogenital region. It most commonly is considered to be a regional variant of verrucous carcinoma, together with oral florid papillomatosis and epithelioma cuniculatum.
(Wikipedia; Medscape; Agarwal, *et al*.).

Condyloma acuminatum is caused by human papilloma virus (HPV) infection. HPV encompasses a family of highly infectious and primarily sexually transmitted double-stranded DNA viruses. The incubation period after exposure ranges from three weeks to eight months. Most infections are transient and cleared within two years.

[Picture Credit: Male Condylomata Acuminatum]

Individuals with condylomata acuminata are at an increased risk for anogenital cancers. In a large Danish cohort study of 16,155 men and 32,933 women, individuals who were diagnosed with condylomata acuminata were at increased risk for anogenital and head and neck cancers for greater than ten years following the diagnosis (anal [SIR for men, 21.5; SIR for women, 7.8], vulvar [SIR, 14.8], vaginal [SIR, 5.9], cervical [SIR, 1.5], penile [SIR, 8.2], and head and neck cancer

[SIR, 2.8], including subsites of head and neck cancer with confirmed HPV association [SIR for men, 3.5; SIR for women, 4.8]).
(Uptodate).

Condyloma acuminatum refers to an epidermal manifestation attributed to the epidermotropic human papillomavirus (HPV). More than 100 types of double-stranded HPV papovavirus have been isolated to date. Many of these have been related directly to an increased neoplastic risk in men and women.

Approximately 90% of condyloma acuminata are related to HPV types 6 and 11. These 2 types are the least likely to have a neoplastic potential. Risk for neoplastic conversion has been determined to be moderate (types 33, 35, 39, 40, 43, 45, 51-56, 58) or high (types 16, 18),[1] with many other isolated types. The picture is complicated by proven coexistence of many of these types in the same patient (10-15% of patients), the lack of adequate information on the oncogenic potential of many other types, and ongoing identification of additional HPV-related clinical pathology.

For example, Bowenoid papulosis, seborrheic keratoses, and Buschke-Löwenstein tumours have been linked to HPV infections though they were previously a part of the differential diagnosis of condyloma acuminata. Bowenoid papulosis consists of rough papular eruptions attributed to HPV and is considered to be a carcinoma in situ. The eruptions can be red, brown, or flesh coloured. They may regress or become invasive. Seborrheic keratoses previously were considered a benign skin manifestation. HPV has been linked to rough plaques indicative of this disease. It has both an infectious and an oncogenic potential. Finally, Buschke-Löwenstein tumour (i.e., giant condyloma) is a fungating, locally invasive, low-grade cancer attributed to HPV.
(E-medicine).

Incidence of Giant Condyloma Acuminatum in South Africa
The National Cancer Registry (2011) does not provide any information regarding this condition.

Risk Factors for Giant Condyloma Acuminatum
The following risk factors may increase a person's chance of developing Giant Condyloma Acuminatum:

- history of human papillomavirus (HPV) infection and other sexually transmitted infections
- long-term exposure to chemicals
- long-term irritation of the penis
- poor genital hygiene
- inability to fully pull back (retract) the foreskin over the glans (phimosis)
- weakened immune system
- low socio-economic status
- drug abuse
- smoking

(Canadian Cancer Society).

Signs and symptoms of Giant Condyloma Acuminatum
Both sexes are susceptible to infection. Overt disease may be more common in men (reported in 75% of patients); however, infection may be more prevalent in women. Prevalence is greatest in persons aged 17-33 years, with incidence peaking in persons aged 20-24 years.

- Smoking, oral contraceptives, multiple sexual partners, and early coital age are risk factors for acquiring condyloma acuminata.
- Generally, two thirds of individuals who have sexual contact with a partner with condyloma acuminata develop lesions within 3 months.
- The chief complaint usually is one of painless bumps, pruritus, or discharge. Involvement of more than 1 area is common. History of multiple lesions, rather than 1 isolated wart, is common.
- Oral, laryngeal, or tracheal mucosal lesions (rare) presumably are transferred by oral-genital contact.
- History of anal intercourse in both males and females warrants a thorough search for perianal lesions.
- Rarely, urethral bleeding or urinary obstruction may be the presenting complaint when the wart involves the meatus.
- The patient's history may indicate presence of previous or other current STDs.
- Coital bleeding may occur. Vaginal bleeding during pregnancy may be due to condyloma eruptions.
- Latent illness may become active, particularly with pregnancy and immunosuppression.
- Lesions may regress spontaneously, remain the same, or progress.
- Pruritus may be present.
- Discharge may be a complaint.

(E-medicine; Canadian Cancer Society).

Diagnosis of Giant Condyloma Acuminatum
It is a sexually transmitted disease with an estimated incidence of about 0.1% in the general population. Human papilloma virus (HPV) has been linked to the aetiopathogenesis of BLT. HPV DNA types 6 and 11 have been most commonly recovered from pathological specimens of BLT, suggesting a pathogenic role.

To confirm histopathologically, deeper tissue must be biopsied to ensure that no malignant cytological characteristics are missed in superficially biopsied specimens. Radical excision of the entire lesion is suggested because it serves the dual purpose of making the diagnosis and helping therapeutically with the highest chances of cure.
(Hindawi).

Treatment of Giant Condyloma Acuminatum
Medical management - A variety of chemotherapeutic modalities have been used with mixed success as adjuvants to surgery or to treat recurrences. The postulated viral origin of these tumours led to the use of interferon with moderate success. One case of vaginal BLT responded to 6 months of interferon-2 alpha with what appeared to be complete resolution. Traditional systemic antitumor agents also have been used. In one case, the patient was treated with bleomycin, cisplatin, methotrexate, and leucovorin after multiple

surgeries for BLT. An autopsy 1 year later found no evidence of active disease. In a separate case, tumour shrinkage was noted after using mitomycin-C and 5-fluorouracil combined with fractionated radiotherapy; unfortunately the patient manifested pulmonary metastases. Etretinate and photodynamic therapy with intravenous porphyrins have been used with some success in treating vaginal BLT. Topical therapy with either podophyllin or 5-fluorouracil has been attempted around the world but, as in our patient's case, is often unsuccessful.

Radiation therapy remains controversial. A Brazilian paper reported total regression of a highly recurrent BLT following radiation therapy. The patient initially was treated with multiple excisions, but continuous recurrences led surgeons to try telecobalt therapy, which resulted in complete resolution of the patient's BLT. Extensive evidence supports the conclusion that tumours behave aggressively after radiation-like anaplastic transformation in oral and plantar verrucous carcinoma. One review recommended avoiding radiation but suggested that, if necessary, administering a large dose of radiation to minimize chances of further mutation may be effective for patients who are poor surgical candidates. We conclude that radiation therapy is a valid treatment modality for managing giant perianal condylomata in selected cases.

Surgical management - The standard approach for managing perianal giant condyloma acuminata is radical surgical excision. Patients with multiple fistulous tracts and purulent discharge may require a temporary loop colostomy. Any compromise regarding radicality is reported to predispose the patient to local recurrence. Some have advocated abdominoperineal resection in cases involving infiltration of the sphincter muscles or rectum. For patients who have BLT with malignant transformation, optimal treatment has not been well-defined.

In a review of 11 patients treated with radical surgery, only 5 remained disease free. This has prompted some authors to recommend preoperative chemoradiotherapy to downstage extensive tumours before performing radical surgery. For classical anal canal cancers, the role of chemotherapy and radiotherapy is now well established, and the combined modality approach is superior to abdominoperineal resection in terms of colostomy-free survival, with many patients maintaining good anal function.

Several case reports describe squamous cell cancers arising from giant condyloma acuminata in patients who respond well to radiotherapy alone or chemoradiotherapy. Butler and colleagues reported on a patient with unresectable disease who received combined modality therapy. A pathological complete response was demonstrated following abdominoperineal resection 32 weeks later. Chu and associates treated one patient's unresectable disease using preoperative chemoradiotherapy followed by abdominoperineal resection and reconstructive surgery. The patient remained disease free 22 months postoperatively. Marsh and colleagues discussed a patient with extensive locoregional disease who was successfully palliated with chemoradiotherapy. Bertram and associates described two patients with inoperable disease whose conditions were successfully down-staged using moderate-dose radiotherapy before they proceeded to surgery.

Wide, radical excision of BLT is the preferred treatment for achieving local control, but excision alone often is ineffective in treating the melanoma variant of BLT. Neoadjuvant chemotherapy may alleviate pain and decrease the tumour burden, but it does not prevent recurrence of the disease. Interferons have been used intralesionally and systemically and have been proven effective in selected cases; however, their adverse effects cannot be ignored.

Troublesome recurrences of BLT occur frequently, and a propensity for infection and fistula formation is common. Adjuvant therapies hold promise, but remain uninvestigated. Regardless of the size and origin of BLTs, gaining early control of the disease using wide, radical surgical excision provides the best overall rate of survival.
(MD All Specialities).

About Clinical Trials
Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials
Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People

who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for

a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or "trial arms": (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

<u>Use of Placebos</u>

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the

study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

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