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CLINICAL REPORT

Penile Intraepithelial Neoplasia: Results of Photodynamic Therapy

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Failure of response to treatment or recurrent disease is often noted in patients with penile intraepithelial neoplasia. Photodynamic therapy has recently been added to the list of treatment modalities used for this diagnosis. Our primary objective was to study the results of photodynamic therapy in the treatment of penile intraepithelial neoplasia in men over the age of 40 years. Ten patients aged 42–82 years with histopathologically confirmed lesions were studied. Lesions initially responded to photodynamic therapy in 7 out of 10 patients. Four of these patients presented no recurrences during a mean follow-up of 35 months, and were completely cleared after 2–8 treatments (mean 4.5 treatments). Three patients presented recurrences after treatment. No patient developed invasive penile cancer (mean follow-up 46.5 months). Photodynamic therapy is an alternative in the treatment of penile intraepithelial neoplasia, although prospective randomized trials are required to provide therapeutic guidelines. ***Key words: Bowen's disease; bowenoid papulosis; erythroplasia of Queyrat; human papilloma virus; lichen sclerosus.***

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Pre-cancerous lesions of the penile epithelium are also known as penile intraepithelial neoplasia (PIN). In 1911, Queyrat (1) introduced the term "erythroplasia of Queyrat" to depict pre-malignant velvety-red lesions of the glans, and Bowen (2) coined the term "Bowen's disease" in 1912 to define single, scaly plaques with histopathological features of squamous cell carcinoma (SCC) *in situ*. Bowenoid papulosis was first described by Lloyd in 1970 (3) and recognized as an entity in 1978 (4). Bowenoid papulosis, characterized by multicentric reddish brown maculopapular lesions of benign appearance on the genitals of young adults, rarely leads to the development of cancer, but progress to SCC has been reported (5). All 3 entities show histopathological signs of SCC *in situ* and are therefore synonymous with PIN (6).

As opposed to the generally benign course of Bowenoid papulosis in younger patients, middle-aged and elderly patients often present solitary PIN lesions with an increased risk of progression to SCC (7). The management of these PIN lesions has proved to be difficult and recurrences are common. Therapeutic alternatives including local excision, Mohs' micrographic surgery, topical 5-fluorouracil (5-FU), cryosurgery, electrocauterization, carbon dioxide (CO_2) laser ablation, interferon and topical 5% imiquimod have been used with varying success rates (7–13). Recently, photodynamic therapy (PDT) has been added to the list of possibilities for the treatment of PIN (14–18), but an insufficient number of patients has been treated to evaluate its potential.

In this study we present our results of PDT in the treatment of PIN in middle-aged and elderly men.

PATIENTS AND METHODS

Patients

Eleven men aged 40 years or above with histopathologically confirmed PIN lesions were treated with PDT between 1999 and 2004 at our dermatological clinic in Göteborg, Sweden. Ten of these patients (aged 42–82 years) were followed up in the present study. One patient who had been treated successfully for a PIN lesion on the glans had developed a cancer of the urethra and was not available for the study. All patients had completed their PDT sessions at the time of inclusion, except for one who was included during ongoing treatment.

A thorough history was taken regarding lichen sclerosus, condyloma, human papilloma virus (HPV) infection, circumcision, smoking habits and previous treatments of PIN. A physical examination of the genitals and groin lymph nodes was performed. Patients with lesions on the glans close to the urethral meatus or with urinary symptoms were referred to a urologist for assessment.

Approval of the study was granted by the local ethics committee. An informed consent document was signed by all subjects included.

Histopathological examination and HPV detection

Punch biopsies performed before treatment in all patients were re-examined by a single histopathologist to verify the diagnosis

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of PIN and determine the evidence of lichen sclerosus and/or signs of HPV infection. New biopsies were taken when recurrences were suspected. Tissue samples for HPV detection were obtained from PIN lesions in 5 patients and from skin areas without remaining lesions after treatment in the other 5 patients. HPV detection and typing was performed using a combination of PCR (19) and reverse hybridization (20) on punch biopsy tissue in 8 patients and on swab samples collected from the surface of treated skin areas in 2. To ensure the quality of the extracted DNA, all samples were analysed and found to be positive for the beta-globin gene (21). Nine of 10 patients were smokers or ex-smokers. None of the patients had undergone neonatal circumcision.

Photodynamic therapy

PDT was performed by application of a topical photosensitizing agent covered by an adhesive occlusive dressing (Tegaderm™, 3M Corp, Neuss, Germany) during 3 h. After removal of dressings and excess cream, the area was illuminated with red light. Anaesthesia with 5% lidocaine-prilocaine cream (EMLA®, AstraZeneca AB, Mölndal, Sweden), intralesional 1% lidocaine (Xylocain®, AstraZeneca AB) or dorsal penile nerve block with 1% lidocaine (Xylocain®) was administered to all patients prior to illumination. Two different PDT methods were used:

ALA PDT. In 9 patients 20% delta-5-aminolaevulinic acid in Unguentum Merck was used as the topical photosensitizing agent, prior to illumination by incoherent light from a Waldmann PDT 1200L lamp (Herbert Waldmann GmbH, Villingen-Schwenningen, Germany) with an emission spectrum of 600–730 nm, a total fluence of 50–80 J/cm^2 and fluence rates of 35–80 mW/cm^2.

Methyl-aminolevulinate PDT. More recently, 3 patients were treated with 16% methyl aminolevulinate cream (Metvix®, PhotoCure ASA, Oslo, Norway) as the topical photosensitizing agent and illumination by red incoherent light from an Aktilite® CL128 LED lamp (PhotoCure ASA, Oslo, Norway) with an emission spectrum of 570–670 nm, a total fluence of 37 J/cm^2 and a fluence rate of 37 mW/cm^2.

Two patients received treatment with both methods.

RESULTS

Treatment

Clearance of PIN lesions was observed initially in 7 of 10 patients treated with PDT (Table I). Four patients were completely cleared from PIN after 2–8 treatments (mean 4.5 treatments) without recurrences during a mean follow-up of 35 months after the first completed series of PDT. Three patients presented recurrences after PDT. Patient 2 recurred after 11 months; patient 5, after 14 months; and patient 7, after 1 month. Patient 4 showed no response to PDT, but had also presented recurrences or poor response to several other therapeutic alternatives. The other 2 patients with incomplete clearance of PIN lesions (patients 1 and 8) only underwent one PDT session. Recurrences occurred after all treatment modalities. No patients developed invasive SCCs during our follow-up (mean follow-up 46.5 months after the first completed series of PDT).

All our patients experienced a certain degree of pain during PDT. This pain was tolerated after anaesthesia using topical lidocaine-prilocaine cream, lidocaine infiltration or dorsal penile nerve block. Superficial erosions were common after PDT, but healed in a matter of days. No scarring or deformities were observed.

HPV infection and other aetiological factors

HPV DNA was not detected in any of the 5 tissue samples obtained from skin areas without remaining lesions after treatment. Three of these samples were collected from skin areas in which PIN lesions had cleared completely after PDT. However, HPV DNA was detected in all 5 patients with PIN lesions present at the

Table I. *Penile intraepithelial neoplasia (PIN) lesions treated with photodynamic therapy (PDT): PIN location and type, human papilloma virus (HPV) types detected, presence of lichen sclerosus (LS), PDT parameters, clinical results and other therapies.*

Pat. no.	Age (years)	PIN location	PIN type	HPV type	LS	PDT method	TF/FR	Times treated	Clinical result	Recurrence	Previous therapy	Therapy after PDT	F/U (m)
1	78	P, Sc	BD	16, 45, 56	No	ALA	80/80	1	Neg	–	–	Ec, Exc	35
2	49	S	BD	16	No	ALA	60/60	2	Pos	Yes	Exc	Exc	38
						m-ALA	37/37	12	Neg	–			
3	52	G	EQ	n.d.	Yes	ALA	50/50	3	Pos	No	Exc	–	35
4	55	P, G	BP	16*	Yes	ALA	35–60/50–60	7	Neg	–	Ec, CO_2,	Ec, CO_2, Im,	92
						m-ALA	37/37	8	Neg	–	5-FU	Exc	
5	82	S, P	BP	n.d.	No	ALA	60/60	2	Pos	Yes	Ec	Ec, Im, Exc	45
6	59	G	EQ	n.d.	No	ALA	40–65/40–65	8	Pos	No	Ec	–	40
7	71	P	BP, BD	16	No	ALA	60/60	2	Pos	Yes	Ec	Ec, Im, Exc	57
							70/70	1	Neg	–			
8	72	P	BD	n.d.	No	ALA	60/60	1	Neg	–	–	Ec, Exc	58
9	65	P, G	BD	n.d.	Yes	ALA	70/70	2	Pos	No	–	–	56
10	42	P	BP	18*	No	m-ALA	37/37	5	Pos	No	–	–	9

P, mucosal prepuce; G, glans; S, shaft; Sc, scrotum; BD, Bowen's disease; EQ, erythroplasia of Queyrat; BP, bowenoid papulosis; n.d., not detected in samples taken after therapy; ALA, PDT with aminolaevulinic acid; m-ALA, PDT with methyl aminolevulinate; TF/FR, total fluence in J/cm^2 and fluence rates in mW/cm^2; Pos, complete clearance; Neg, incomplete clearance; Ec, electrocauterization; Exc, local excision; CO_2, carbon dioxide laser ablation; 5-FU, 5-fluoro-uracil; Im, 5% imiquimod; F/U, follow-up; m, months.
*Tissue sample collection before PDT.

time of sample collection. In these cases, tissue samples were obtained from remaining PIN lesions after PDT in patients nos. 1, 2 and 7 and from PIN lesions before PDT in patients nos. 4 and 10. HPV DNA positive tissue samples were not collected from any areas afflicted by lichen sclerosus. HPV 16 was detected in 4 patients and HPV 18 was found in another. In patient 1, HPV 16 was detected in biopsy material from the prepuce and HPV types 45 and 56 were found in tissue from a PIN lesion of the scrotum. Microscopic verification of lichen sclerosus was observed in 3 patients (patients 3, 4 and 9).

DISCUSSION

Until now, only a few case reports have been published concerning the treatment of PIN with PDT (14, 15, 17, 18). Our study on 10 patients is thus the largest series published to date. Prospective randomized trials are necessary to provide therapeutic guidelines for treating PIN with PDT, since the number of sessions required is uncertain.

In our study, PIN lesions were completely cleared with PDT in 7 of 10 patients. Four of these presented no recurrences during a mean follow-up of 35 months and cleared after at least 2 treatments (range 2–8 treatments). Three patients had recurrences after treatment. Two lesions that resisted clearance were treated with only one session, which was probably insufficient to assess the possible results. A larger number of patients should be treated in order to observe any differences in how erythroplasia of Queyrat, Bowen's disease and bowenoid papulosis respond to PDT. New topical photosensitizing agents and light sources are constantly being introduced and may improve results.

Comparative trials on the effectiveness of established therapeutic alternatives have not been performed, but some authors consider surgery (recurrence rate 14–33% in 5 years) and CO_2 laser ablation (recurrence rate 0–33%) to be first-line therapies (7). Relapse and progress to invasive cancer can occur independently of the treatment provided.

If PIN lesions are left untreated, the risk of progression to invasive penile cancer is estimated to be 5–10% (22). Although unusual, development of lymph node metastasis has been reported after treatment of PIN with circumcision combined with 5-FU (23). Progress of PIN to invasive penile cancer has been reported after CO_2 laser ablation (24) and after PDT combined with topical 5-FU (25).

HIV-infected individuals have a greater relative risk of developing PIN lesions (26). However, no patients in our study were tested because we had no clinical or anamnestic suspicion of HIV infection. The known association between PIN lesions and HPV infection (7) was confirmed in our study, as HPV DNA was detected in all 5 tissue samples obtained from PIN lesions. However, HPV DNA was not detected in those samples collected from skin areas completely cleared of PIN after treatment. This could indicate that PDT and other treatments may suppress or eliminate HPV infection, although the amount of cases is insufficient to draw any firm conclusions. All HPV types found were known mucosal high-risk HPV types (4, 27).

Lichen sclerosus was confirmed in 30% of our patients with PIN, which is a result comparable to the frequency of lichen sclerosus in patients with penile SCC (28–30). Smoking, which has also been described as a risk factor for invasive penile cancer (31), was very common among our patients (90%). Although further studies are necessary, smoking should be discouraged (32). Lack of neonatal circumcision, as noted in all patients in our study, is a known risk factor for PIN (33) and penile cancer (31).

Individual assessment of each patient with PIN is required to provide optimal management. The choice of therapy should be based on the size and distribution of the lesions, while taking into account the experience of the physician. All PIN lesions in our study were managed with non-mutilating treatment alternatives. The ideal therapeutic modality is yet to be established, but penis-sparing therapy should be the aim. This recommendation is supported by the fact that none of our patients developed invasive SCCs during follow-up. We conclude that PDT should be added to the list of therapeutic alternatives in the treatment of PIN.

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