Digestive and Liver Disease 48 (2016) 806–811

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

High-grade anal intraepithelial neoplasia: Progression to invasive cancer is not a certainty

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ARTICLE INFO

Article history:
Received 21 January 2016
Accepted 15 March 2016
Available online 28 March 2016

Keywords:
Age
Anal cancer
Cancer
Healing
High-grade intraepithelial neoplasia
HIV
Human papillomavirus
Smoking

ABSTRACT

Background: The incidences of high-grade anal intraepithelial neoplasia (HSIL) and superficially invasive squamous cell carcinomas (SISCCA) related to human papillomavirus (HPV) have increased. These lesions can progress to invasive anal cancer. The aim of the study was to assess the clinical outcome with a special focus on the healing rate.
Methods: Forty-six consecutive patients (M/F: 35/11; HIV+: 30) with histologically proven HSIL lesions ($N = 41$) or SISCCA ($N = 5$) were enrolled in a follow-up survey.
Results: Of the 46 patients, 40 were treated by excision ($n = 9$), electrocoagulation ($n = 13$), topical treatment ($n = 2$) or combined strategies ($n = 16$). After a mean follow-up of 35 (27–43) months, only one patient progressed to an invasive cancer. Regression and healing were observed in 14 (30%) and 15 (33%) patients. The cumulative probabilities of healing were 14%, 49% and 74% after 1, 3 and 5 years. None of the current smokers healed. Heterosexual patients, sexual abstinence, patients older than 44 years old, non-smokers, patients without any past history of condyloma and those with less than 2 high-risk HPVs at baseline were more likely to heal.
Conclusion: Progression to invasive cancer is a rare event. Large, prospective cohort studies are needed to plan coherent strategies for both follow-up and treatment.

1. Introduction

The incidences of anal cancer and its putative precursor (high-grade squamous intraepithelial lesions: HSIL) have greatly increased in recent decades [1–3] particularly in special population subgroups: men who have sex with men (MSM), those infected with human immunodeficiency virus (HIV), and women with previous cervical human papillomavirus (HPV)-related disease [4].

Anal carcinoma increased from 0.2 to 0.5/100 000 person-years among men and from 0.7 to 1.3/100 000 person-years among women from 1982 to 2012 [3].

Regarding cervical cancer, it is widely recognized that HSIL and superficially invasive squamous cell carcinoma (SISCCA) can preclude invasive cancer. The latter is defined as a nearly stage tumours ≤10 mm, corresponding to HSIL which has an invasive depth of ≤3 mm from the basement membrane of the point of origin, with horizontal spread of ≤7 mm at its maximal extent [5]. Both types of lesions are induced by persistent infections of carcinogenic HPV [6,7]. Conventionally, they are likely to progress to an invasive cancer [5]. Little is known about the natural history of anal HPV infections and HSIL. One study estimated a HSIL regression rate of 23.5% per year [8].

The lack of data about the natural progression of HSIL and SISCCA to invasive cancers has led to unclear and controversial therapeutic strategies. Management of HSIL varies according to the doctor's expertise, ranging from expectant management with close surveillance [9,10] to surgical treatment [11], topical application of chemotherapeutic agents [12] or photodynamic therapy [13]. To date, the recommended treatment for SISCCA is radiotherapy, but it has been associated with anatomical and functional side effects unless effective [14–16]. After we collected the data of consecutive

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http://dx.doi.org/10.1016/j.dld.2016.03.011
1590-8658/

patients with histologically proven HSIL, the aim of this study was to assess the clinical outcome with a special focus on the healing rate.

2. Patients and methods

2.1. Patients

This cross-sectional study was conducted in a single tertiary gastroenterology unit (Rennes University Hospital, France) using the records of a central database. All patients with histories of HSIL (only AIN3 in the former classification) or SISCCA proven on anal biopsy, from March 2002 to May 2014, were invited to participate in a new evaluation. Medical records, using both retrospective (2002–2006) and prospective (2007–2014) databases, were extracted with special emphases on MSM and women with HPV-related genital lesions and HPV-related lesions, as well as smoking habits and immunosuppressant use. Data about life style and HIV disease were collected using a standardized questionnaire sent to the patient: gender, age, sexual activity, past history of sexually transmitted infections, and HIV status, including CDC stage, highly active antiretroviral therapy (HAART), CD4 cell count, and HIV viral load. Patients who did not respond to the questionnaire were solicited by phone and by sending new mail. To identify clinically relevant events that might interfere with clinical outcome, each treatment procedure was noted: surgery (specifying with or not healthy margins); destruction of the lesion (including electrocoagulation and infrared); or application of imiquimod. We also reported the periods of duration of therapies and the number of surgical events.

Most of the patients were evaluated every 6 months to ensure the lack of progression. Any abnormalities were evaluated by high-resolution anoscopy (HRA) (performed using 5% acetic acid and Lugol's solution to magnify the visualization of abnormal anal tissue), and multiple targeted biopsies were performed (to limit heterogeneity and to ensure that the highest grade of dysplasia was identified). Random biopsies were also collected from regions that appeared normal at the level of the dental line. Finally, control biopsies of previous HSIL sites were realized at the end of the follow-up to determine whether the lesion persisted (HSIL), was down-staged (LSIL) or had healed (normal histology).

2.2. HPV DNA detection and genotyping

Before anoscopy, one Dacron swab was collected from the anal canal and was immediately suspended in Thin Prep PreservCyt medium (Hologic, Inc. Bedford, MA, USA). This sample was sent for virological analysis. Specimens were maintained at +4 °C before processing for analyses and then were aliquoted and stored at −80 °C. DNA testing was performed using the PreservCyt medium: 200 μL were used for DNA extraction on MagNA Pure LC (Roche, Bâle, Switzerland). Anal specimens were tested for 35 HPV genotypes with CLART Human Papillomavirus 2 (Genomica, Madrid, Spain), a commercial kit for the detection of 15 low risk HPV (6, 11, 40, 42, 43, 44, 54, 61, 62, 71, 72, 81, 83, 84, 89), and 20 high risk HPV strains (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, 82, 85). The tests included a cellular control and an internal control. Microarray studies were analyzed using a Clinical Arrays Reader (Genomica). A sample of 2 mL of each liquid-based medium was then frozen at −80 °C. The Ahr-HPV DNA test was considered positive if at least one hr-HPV genotype was detected.

2.3. Follow-up

The initial histology reporting HSIL or SISCCA was the first point of follow-up, and the last point was the most recent histology. Follow-up continued until June 30, 2014. Loss to follow-up was defined by the lack of response to any questionnaire or the inability to find the patient.

Most of the patients were evaluated every 6 months to ensure the lack of progression. Any abnormalities were biopsied. Regression was defined by Regression was defined by the stable regression of HSIL to a less invasive state (LSIL or normal) from the first change to the last biopsy of the follow-up. Regression had to be stable throughout the follow-up. In the regression group, we distinguished down-staged (LSIL) and healed (normal histology) states.

Progression was defined by the occurrence of SISCCA for patients with HSIL or invasive carcinoma for patient with SISCCA or HSIL.

The patients were separated into three groups according to their follow-up status: regression and/or healing; persistence of HSIL/SISSCA; or progression to invasive cancer.

2.4. Ethics

The database was authorized by the national regulatory institution, Commission Nationale Informatique et Liberté, and the study was approved by our institutional ethical committee (October 17,

Table 1
Characteristics of the study group ($N = 51$).

	N		%
Sex			
Male	37		73
Female	14		27
Age (years, mean)		48 ± 2.1	
BMI (mean)		24 ± 1.2	
Past history of STI not related to HPV			
Yes	18		35
No	33		65
Past history of condyloma/HPV infection			
Yes	24		47
No	27		53
Past history of cervical cancer or conization			
Yes	05		36
No	09		64
Past history of LSIL			
Yes	07		14
No	44		86
HIV			
Yes	33		65
No	18		35
MSM			
Yes	32		86
No	5		14
Immune-suppression treatment[a]			
Yes	03		6
No	48		94
Smoking			
Current and/or past	25		49
Never	26		51
Past history of anal sex			
Yes	37		72.5
No	12		23.5
Unknown	2		4
Total number of sexual partners			
<5	4		7.5
(5–10)	9		17.5
(10–50)	14		27.5
>50	18		35.5
Unknown	6		12
Sexually active life			
Yes	30		59
No	19		37
Unknown	2		4

BMI, body mass index; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus, HPV, human papillomavirus; LSIL, low grade superficial intra-epithelial lesion; MSM, men who have sex with men; STI, sexually transmissible infection.

[a] One Horton disease and two renal transplantations.