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# Giant condylomata acuminata of Buschke and Lowenstein: A peristomal variant

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## ABSTRACT

**INTRODUCTION:** Giant condylomata acuminata (GCA) is a rare, locally invasive tumour that may undergo malignant transformation. It was first described a HPV-induced penile tumour which clinically resembled both a squamous cell carcinoma and condyloma acuminatum, often arising from a pre-existing warty lesion. We describe a case of peri-stomal GCA transformation into invasive squamous cell carcinoma (SCC), which is, to our knowledge, the first report of this in the literature.

**PRESENTATION OF CASE:** A 74 year old gentleman developed an acuminata, papillomatous peristomal eruption around a fifty year old ileostomy, with biopsies of the eruption showing reactive changes. Two years later, he developed ulcerating plaques affecting the previously papillomatous areas and an erythematous nodular lesion involving the superior part of the ileostomy and adjacent skin. Histological examination of the ileostomy lesion showed focal small islands of atypical squamous epithelium, and moderately differentiated invasive squamous cell carcinoma was shown in the excised tissue subsequently. Human papillomavirus (HPV type 16), p16 and p53 tumour suppressors were positive in the peri-stomal skin sample.

**DISCUSSION AND CONCLUSIONS:** Recurring, changing papillomatous lesions in the peristomal area should be reviewed with a high index of suspicion in relation to GCA tumours as they can progress to invasive squamous cell carcinomas.

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## 1. Introduction

Proctocolectomy and permanent ileostomy formation became a standard treatment for severe ulcerative colitis (UC) following the introduction of the eversion, terminal ileostomy in the 1950s.<sup>1</sup> It is therefore not uncommon to see patients with an ileostomy formed more than 50 years previously, particularly for UC. The formation of adenocarcinoma is reported in these long-standing ileostomies, often arising in areas of bowel metaplasia of the peristomal skin,<sup>2–3</sup> with a suggestion that the hyperproliferation from regenerative epithelium over long periods due to chronic irritation predisposes to malignant transformation.<sup>2</sup> Primary squamous carcinomas affecting ileostomies, however, are extremely rare.<sup>4</sup> We

describe a case of peri-stomal giant condylomata acuminata (GCA), a rare, locally invasive tumour, transforming into invasive squamous cell carcinoma (SCC). We discuss the clinical features of this case together with the role and importance of oncogenic human papillomavirus infection in squamous cell carcinoma pathogenesis.

## 2. Presentation of case

A 74 year old man with a history of UC underwent pan-proctocolectomy and ileostomy formation in 1963. In early 2009, he began to have intermittent peristomal overgrowth and superficial ulceration, which was successfully treated with sucralfate powder. At presentation to dermatology in 2011 he was experiencing leakage because of a red, exudative verrucous plaque at the 7–9 o'clock position (Fig. 1a). He had a short stoma that led to leaks around the stoma appliance and had atrophic peristomal skin. Surgical revision of the stoma was considered but the patient and his surgical team were keen to consider a conservative approach first. The plaque was curetted under local anaesthetic and subjected to histological examination which confirmed benign reactive changes only. The patient was followed up regularly and over the next 2 years he

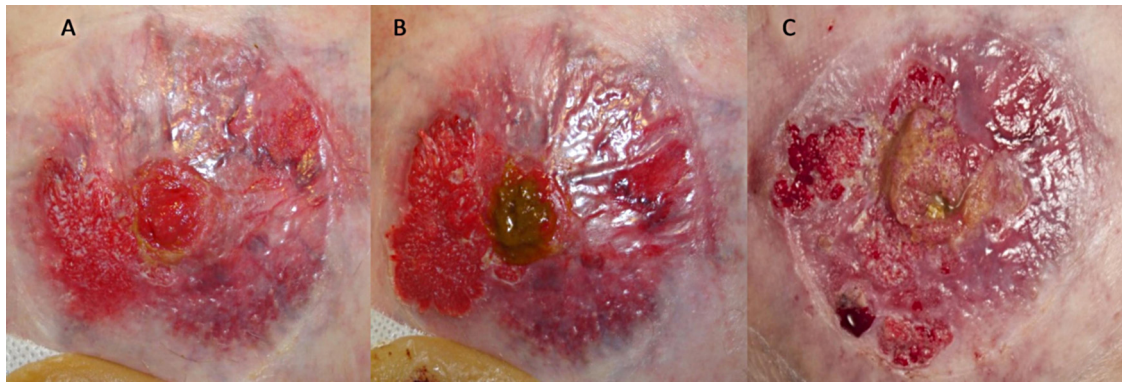
**Abbreviations:** GCA, giant condylomata acuminata; SCC, squamous cell carcinoma; HPV, human papillomavirus; UC, ulcerative colitis.

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**Fig. 1.** (A) At presentation; superficial erosion at the 2 o'clock position and an exudative verrucous plaque at the 7–9 o'clock position. (B) Nine months later the plaque has recurred and is more obviously verrucous with acuminate papules. (C) Warty, papillomatous lesions affecting the ileostomy and peristomal skin.

had the procedure repeated 3 times because of recurrence of this acuminate, verrucous peristomal eruption (Fig. 1b). On review in summer 2013 there was a clear difference in the clinical appearance of the peristomal skin (Fig. 1c) with papillomatous and ulcerating plaques affecting three quarters of the circumference of the mucocutaneous junction of the ileostomy, with associated erythematous, hyperkeratotic scaling. There was a new tumid lesion involving the stoma itself at the 11–1 o'clock position. Biopsies were taken from this tumour and the larger of the ulcerating plaques. Histological examination showed hyperplastic epithelium, parakeratotic scale, atypia and focal small islands of atypical squamous epithelium highly suspicious of invasive squamous cell carcinoma (Fig. 2). Given the preceding verrucous plaque this appeared to be a peristomal equivalent of the Buschke-Lowenstein tumour usually found in the ano-genital region.

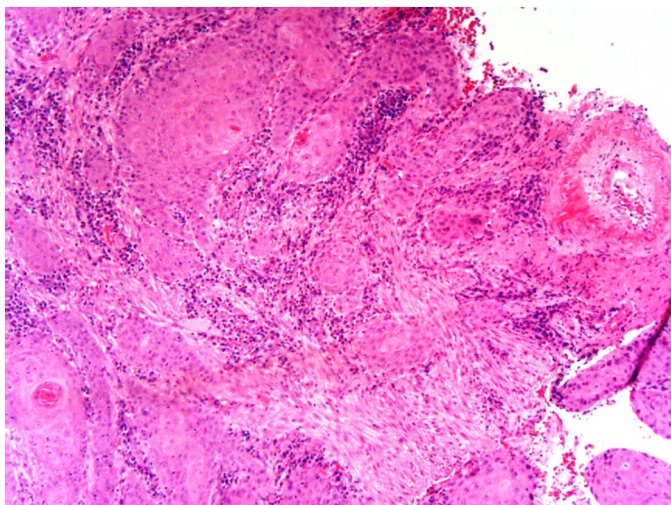
A staging CT scan was performed, which showed no significant nodal disease. A PET-CT scan showed marked increase in metabolic activity at the distal end of the ileostomy, in a right inguinal node, and in the right posterior thigh.

He was referred to the multi-specialty, surgical oncology team at a tertiary referral centre, where a wide excision of his ileostomy and abdominal wall reconstruction was performed along with a resiting of the stoma and an abdominoplasty. Histopathology of the excised tissue of the ileostomy and the abdominal wall showed moderately differentiated invasive squamous cell carcinoma up to a maximum thickness of 13 mm (Fig. 3). Tissue from both the stoma

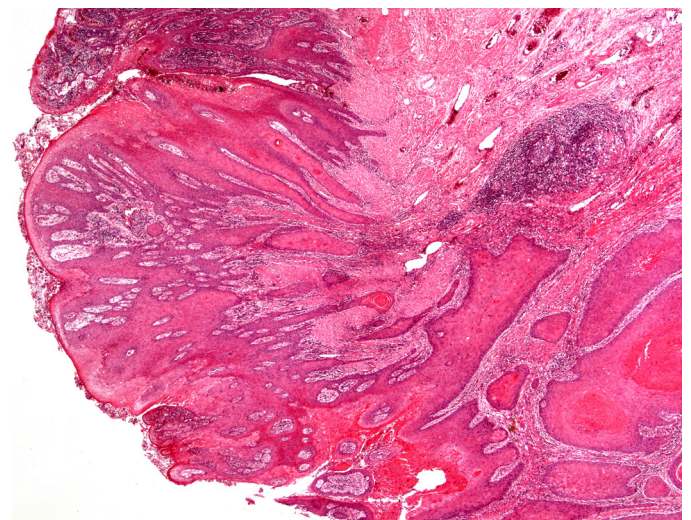
and the abdominal wall were sent for human papillomavirus (HPV) PCR testing, with the former sample testing positive for HPV type 16 at a low level. Immunohistochemistry revealed a positive tumour suppressor p53 in the basal and parabasal layer of non-neoplastic hyperplastic squamous epidermis, as well as patchy positive areas in the periphery of the invasive carcinoma. Staining for p16 was also diffusely positive in the non-neoplastic hyperplastic squamous epidermis but this was negative in the squamous cell carcinoma (Fig. 4).

### 3. Discussion

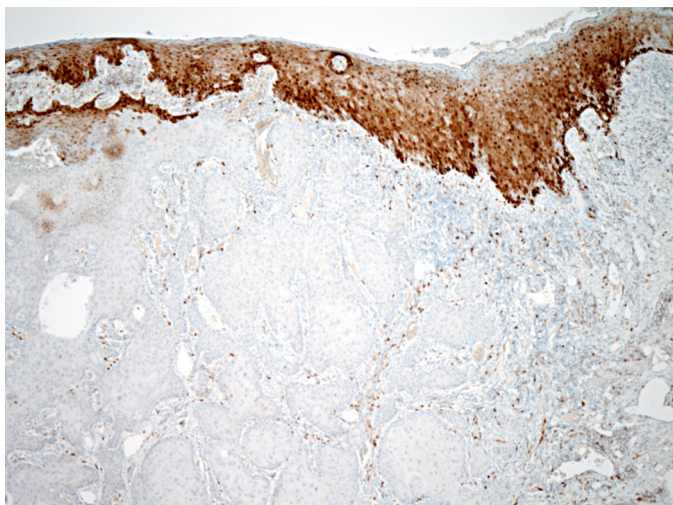
Adenocarcinoma occurring in the peri-ileostomy skin is a well-recognised complication of longstanding ileostomies.<sup>2–3</sup> Primary squamous carcinoma by contrast, is apparently far less common with only 5 previous cases reported, all of which have occurred in ileostomies fashioned at least 26 years previously.<sup>4–8</sup> Ejtehadi et al.<sup>4</sup> have recently reviewed these cases, which are universally in patients with a long-standing ileostomy formed for the management of inflammatory bowel disease. They all presented with a sizeable tumour or ulcer. Our patient was attending a specialist dermatology/stoma service for a presumed irritant reaction such that we were able to identify a potentially premalignant, verrucous, papular stage in the evolution of SCC.



**Fig. 2.** Histology of the biopsy to the ileostomy, showing squamous atypia (H&E, magnification 20 $\times$ ).



**Fig. 3.** Histology of the resected peristomal skin showing squamous cell carcinoma in situ on the upper left and squamous cell carcinoma invading into the subcutis on the right (H&E, magnification 40 $\times$ ).



**Fig. 4.** Immunohistochemistry staining for p16, showing diffuse positive staining in the non-neoplastic hyperplastic squamous epidermis (p16, magnification 40 $\times$ ).

The Buschke–Lowenstein tumour (also known as a giant condylomata acuminata/GCA) is a rare, locally invasive tumour arising from a pre-existing warty lesion, often described as an exophytic, cauliflower-like growth.<sup>9</sup> This neoplasm was first described by Buschke and Lowenstein in 1925 to describe a penile tumour which clinically resembled both a squamous cell carcinoma and condyloma acuminatum, but had clinical and histological differences from both of these entities.<sup>10</sup>

Whilst highly destructive locally, the GCA tumour rarely metastasizes. The malignancy is associated with human papillomaviruses (HPV), in particular HPV-6 and HPV-11.<sup>11–12</sup> Characteristics of the tumour include malignant transformation and a high rate of recurrence, along with ulceration and infiltration into deep tissues.<sup>13</sup> Sites that are typically affected include the penis, perianal region, vulva, vagina, rectum, scrotum, perineum and the bladder.<sup>9</sup> However, to our knowledge there has been no previous description of a GCA-like tumour occurring in relation to a stoma.

The clinical differential diagnosis in this case is a Marjolin's ulcer, a well-differentiated squamous cell carcinoma arising from a chronic wound, often occurring after a latent period of 30 years on average.<sup>14</sup> The key difference between the two diagnoses is the aggressive nature and high metastatic rate of a squamous cell carcinoma arising within a Marjolin's ulcer, reported to be 27.5% in a review.<sup>15</sup> The history of a recurring, papillomatous lesion preceding the development of an invasive squamous cell carcinoma in this case is more in keeping with a GCA tumour rather than a Marjolin's ulcer.

In relation to the presence of HPV and the development of squamous cell carcinoma, it is thought that the products of two viral genes, E6 and E7, inactivates p53 and Rb (retinoblastoma protein), which are cellular tumour suppressors, and upregulates the expression of p16 in high risk HPV-related cancers. It has been shown that in anal carcinoma overexpression of p16 was strongly associated with high-risk HPV infection.<sup>16</sup> The association of p53 and HPV is less clear, as some suggest p53 accumulation is associated with the presence of HPV,<sup>17</sup> while others have not found any association between HPV (type-16) and p53 immunostaining.<sup>18</sup> Thus, in this case the presence of p16 in the surrounding non-neoplastic squamous tissue is in keeping with the finding of a high-risk HPV infection driven malignancy, while the significance of p53 positive immunostaining is unclear. The mechanism whereby HPV is transmitted is unclear. There is a hypothesis that peripheral blood lymphocytes may act as a mediator of HPV infection to peripheral tissues, as it was shown in a study that the E6 oncoprotein was

expressed in both the endothelial cells and the tumour infiltrating lymphocytes of HPV16 DNA positive colorectal tumours.<sup>19</sup>

The standard treatment for a resectable invasive squamous cell carcinoma is surgical excision with wide margins. Management for a GCA without squamous cell carcinoma transformation is less straightforward. Wide surgical excision is a recommended and effective option where possible.<sup>9,13</sup> Medical treatments are often considered either in combination with surgical treatments to achieve adequate tumour clearance, or as a sole treatment in non-resectable tumours. Case reports have suggested that both intralesional and systemic interferon- $\alpha$ 2b were successful in treating GCA, and it is thought that this had both an immunostimulatory and antiviral effect on the tumour.<sup>20</sup> A case report combining the triple modalities of surgical excision, topical imiquimod and oral acitretin obtained continued clearance at 6 months.<sup>9</sup> Imiquimod has also been used in conjunction with CO<sub>2</sub> laser ablation with success.<sup>21</sup>

Papular irritant reactions are common around ileostomies particularly if there are recurrent leaks of faeces or urine.<sup>22</sup> They typically present as acanthotic or hypergranulating papules rather than the plaque composed of acuminate papules seen in our case. Ulceration is similarly common and is usually a result of minor trauma. Non-resolving ulceration or new papules should be biopsied for histological examination. In well-differentiated and verrucous carcinomas however, a sample biopsy may not be diagnostic and can be misleading<sup>23</sup> so that it is possible that the initial biopsies in our case were unrepresentative.

#### 4. Conclusion

The invasive squamous cell carcinoma in this case has arisen from a variant of verrucous carcinoma, akin to the GCA of Buschke–Lowenstein. Although these tumours are rare, morbidity and mortality may be reduced with a high index of suspicion from the clinician when faced with recurring, changing papillomatous lesions in the peristomal area. A deep excision biopsy may be warranted to rule out any foci of squamous cell carcinoma within the lesion. If identified, the treatment should be of wide excision which will usually require repositioning of the stoma and significant abdominal wall reconstruction providing there is no evidence of metastatic disease.

#### Conflict of interest

None reported.

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This study was not supported by a sponsor.

#### Ethical approval

Written consent obtained.

#### Author contributions

Drs Yiu, Lyon had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Yiu, Ali, Lyon. Acquisition, analysis and interpretation of data: Yiu, Ali, Mowatt, Wilson, Lyon. Drafting of the manuscript: Yiu, Ali. Critical revision of the manuscript for important intellectual content: Yiu, Ali, Mowatt, Wilson, Lyon. Administrative, technical or material support: Yiu, Lyon. Study supervision: Lyon.

### Key learning points

- Giant condylomata acuminata (GCA) is a rare, locally invasive tumour that may undergo malignant transformation.
- Primary squamous carcinoma occurring in peri-stomal skin is rare. This is the first known report of a peristomal GCA tumour followed by progression into a squamous cell carcinoma.
- Long-term follow-up and having a high index of suspicion regarding malignancy in patients with long-standing stomas and peri-stomal lesions is very important.

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