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Characterizing the immune checkpoint marker profiles of cutaneous squamous cell carcinomas in patients with hidradenitis suppurativa

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LETTER TO THE EDITOR

Characterizing the immune checkpoint marker profiles of cutaneous squamous cell carcinomas in patients with hidradenitis suppurativa

Dear Editor

Hidradenitis suppurativa (HS) is an inflammatory skin disease characterized by recurring abscesses, nodules and tunnels with predilection for intertriginous locations. The reported rate of cutaneous squamous cell carcinoma (cSSC) complicating HS in a single-centre retrospective report of 227 HS patients was 4.6%,[1] but of 1139 patients in our prospective registry at the University of North Carolina at Chapel Hill (UNC-CH) from 10 August, 2018 to March 2022, we have encountered no cases, suggesting rates may be lower. Poor clinical outcomes are typically due to advanced presentation, similar to Marjolin's ulcers.[2]

Immune checkpoint inhibitors for treatment of advanced cSCC have garnered recent interest.[3] Program death ligand 1 (PD-L1) on tumour cells binds with program death 1 (PD-1) receptor on T cells to inhibit immune activation, helping tumours evade cytotoxic destruction.[4] 25%–80% of locally aggressive and advanced cSCCs express PD-L1 in varying levels.[5] Pembrolizumab, a PD-1 inhibitor, and cemiplimab, an FDA-approved PD-1 receptor antagonist, have shown efficacy treating recurrent, metastatic and advanced SCC.[6] Lymphocyte activation gene 3 (LAG-3) has also attracted attention due to its relationship with the PD-L1/PD-1 axis.

This investigation presents the unique immune checkpoint marker profiles of five patients with cSCC arising from chronic HS lesions.

Following ethics board approval at the UNC-CH School of Medicine, five patients with cSCC in skin affected by HS between January 2000 and December 2018 were identified within UNC Health, Henry Ford Hospital System and Mayo Clinic databases. After chart review confirming that SCC involved HS skin, tumour histology was assessed in haematoxylin and eosin staining and immunohistochemistry as outlined previously by our research group in the Materials and Methods section of Wu et al.[5]

The average age at diagnosis was 54.8 years, four patients were male, and four patients were White (Table 1). All tumours arose in the groin and/or buttocks. Four of five patients underwent wide local excision with margins, and one was referred for palliative care. Four patients experienced recurrence before death, and one was lost to follow-up.

Three of five tumours expressed PD-L1, and all had tumour-associated inflammation, TILs and PD-L1 positivity of the TAI. PD-L1-negative carcinomas had higher LAG-3-positive lymphocyte counts than PD-L1-positive carcinomas (Table 1). Representative immunohistochemical images for Case 1 are displayed in Figure 1. Lymphocyte-associated immune checkpoint markers were also characterized (Table 1).

The demographic characteristics and poor outcomes in this series align with prior publications of HS-derived SCC.[7] Immune marker profiles and the presence of TAIs and TILs in most samples were consistent with previous reports on non–HS-derived cSCC.[5] Importantly, immune markers can be differentially expressed over time, as demonstrated in two chronologically separated samples from case two. Three of five tumours expressed PD-L1, suggesting that PD-L1/PD1 inhibitor therapy may be useful in advanced HS-derived cSCC tumours positive for PD-L1.

Pathways involving LAG-3 are not well understood but appear to prevent autoimmunity.[8] In malignancy, LAG-3 expression may cause immune 'exhaustion' with decreased function of T cells and is linked to resistance to PD-1 inhibitors.[9] In tumour models, blockage of both LAG-3 and PD-L1 was successful in reversing exhaustion.[8]

Lymphocytes from case five had the lowest level of PD-1 expression but the highest level of LAG-3 expression (Figure 1). Cases not positive for PD-L1 (Case four and five) had lymphocytes that were highly positive for LAG-3. The tumours, therefore, would likely be resistant to PD-1 inhibitor therapy,[10] but LAG-3 inhibition may present an alternative treatment path.

Although HS-derived cSCC is relatively rare, given the poor prognosis and paucity of treatment options, characterization of immune checkpoint markers before timely inclusion of immunotherapy can be considered when managing cases.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST

None to disclose.

TABLE 1 Patient information and tumour characteristics

Patient information								
Case number	**Age at diagnosis (years)**	**Sex**	**Race**	**BMI (kg/m^2)**	**Smoking status**	**Survival time after SCC diagnosis**	**Primary tumour location**	**Biopsy site (Site of Immune Checkpoint Marker Analysis)**
1	51	F	W	17.3	Former	8 years	Vulva, perineum, right thigh, posterior wall of vagina	Right proximal thigh
2	52	M	W	27.8	Never	6 years	Right buttock, extension into perineum, scrotum, right thigh, inguinal canal	Peri-scrotal skin
3	52	M	W	26.6	Never	3 years	Left and right buttocks, proximal left thigh, sacrum	Right buttock
4	58	M	AA	25.6	Former	Unknown	Left buttock	Left buttock
5	61	M	W	38	Current	1 month	Right medial buttock	Right medial buttock

Tumour characteristics & immune checkpoint markers									
Case number	**Tumour**	**Broder grade[a]**	**TAI**	**TILS**	**PD-L1 Tumour**	**PD-L1 TAI**	**CD8 (cells/mm^2)**	**PD-1 (cells/mm^2)**	**LAG-3 (cells/mm^2)**
1	Mod Well	1	Brisk	Brisk	Pos High	Positive	3000	107	79
2	Mod Well	1	Non-brisk	Non-brisk	Pos High	Positive	713	239	51
2a[b]	Mod	2	Non-brisk	Non-brisk	Pos High	Very focal	505	44	40
3	Mod	2	Non-brisk	Non-brisk	Pos Low	Positive	760	369	31
4	Mod poor	3	Brisk	Brisk	Neg	Positive	1171	233	111
5	Mod	2	Non-brisk	Non-brisk	Neg	Focal	401	52	456

Abbreviations: AA, African American; F, Female; LAG-3, Lymphocyte Activation Gene 3; M, Male; Mod, Moderate; PD-1, Programmed cell death protein 1; TAI, Tumour-associated inflammation; TILS, Tumour-infiltrating lymphocytes; W, White.

aGrades are 1, 2, 3 and 4.

[b]Recurrent tumour (5 years after original Case 2 tumour).

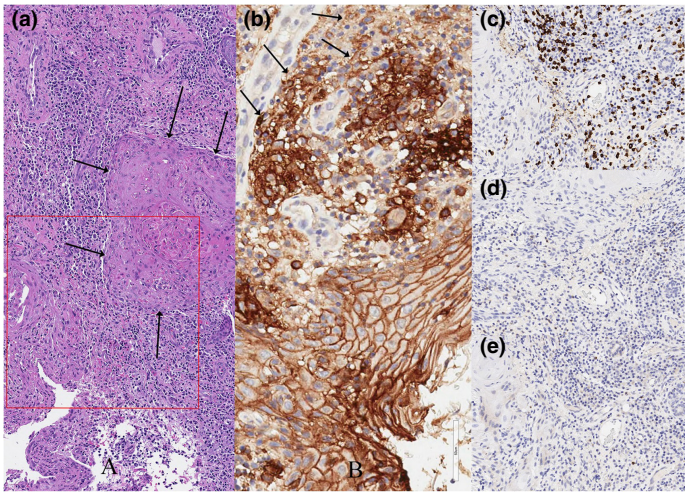

FIGURE 1 (a) Squamous cell carcinoma (arrows) has surrounding tumour associated inflammation. The red square illustrates the size of region of interest used for lymphocyte counts (H&E 15×). (b) Squamous cell carcinoma has intense surface staining for PD-L1 (lower half of image). The arrows identify PD-L1 positive tumour associated inflammatory cells (PD-L1 DAB 20×). (c) CD8 positive lymphocytes (CD8 DAB 20×). (d) PD-1 positive lymphocytes (PD1 DAB 20×). (e) LAG-3 positive lymphocytes (LAG 3 DAB 20×).

DATA AVAILABILITY STATEMENT

Research data are not shared.

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