

- [12] Hassel JC. Ipilimumab plus nivolumab for advanced melanoma. *Lancet Oncol.* 2016;17:1471–1472.
- [13] Hodi FS, Chesney J, Pavlick AC, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. *Lancet Oncol.* 2016;17:1558–1568.
- [14] Valsecchi ME. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med.* 2015;373:1270.
- [15] Ott PA, Hodi FS. Talimogene laherparepvec for the treatment of advanced melanoma. *Clin Cancer Res.* 2016;22:3127–3131.
- [16] Kaufman HL, Kim DW, DeRaffele G, et al. Local and distant immunity induced by intralesional vaccination with an oncolytic herpes virus encoding GM-CSF in patients with stage IIIc and IV melanoma. *Ann Surg Oncol.* 2010;17:718–730.
- [17] Quezada SA, Peggs KS, Curran MA, et al. CTLA4 blockade and GM-CSF combination immunotherapy alters the intratumor balance of effector and regulatory T cells. *J Clin Invest.* 2006;116:1935–1945.
- [18] Hodi FS, Lee S, McDermott DF, et al. Ipilimumab plus sargramostim vs ipilimumab alone for treatment of metastatic melanoma: a randomized clinical trial. *JAMA.* 2014;312:1744–1753.
- [19] Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *JCO.* 2015;33:2780–2788.
- [20] Killock D. Skin cancer: T-VEC oncolytic viral therapy shows promise in melanoma. *Nat Rev Clin Oncol.* 2015;12:438.
- [21] Puzanov I, Milhem MM, Minor D, et al. Talimogene laherparepvec in combination with ipilimumab in previously untreated, unresectable stage IIIB-IV melanoma. *J Clin Oncol.* 2016;34:2619–2626.
- [22] Pembrolizumab with or without talimogene laherparepvec or talimogene laherparepvec placebo in unresected melanoma (KEYNOTE-034) [updated 2017 Mar]. Available from: <https://clinicaltrials.gov/show/NCT02263508>
- [23] Weber JS, Gibney G, Sullivan RJ, et al. Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, phase 2 trial. *Lancet Oncol.* 2016;17:943–955.
- [24] Pilot study of sequential ONCOS-102, an engineered oncolytic adenovirus expressing GMCSF, and pembrolizumab in patients with advanced or unresectable melanoma progressing after programmed cell death protein 1 (PD1) blockade 2016 [updated 2017 Mar]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03003676>

LETTER TO THE EDITOR

The concept of immunocompromised district might explain the carcinogenic progression in hidradenitis suppurativa

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We read with great interest the case report recently published in *Acta Oncologica* by Zhang and Tan [1], which describes a 59-year-old man with a 30-years history of gluteal and perianal hidradenitis suppurativa (HS), who developed a squamous cell carcinoma (SCC). Zhang and Tan state that more than 70 cases of SCC have been documented among patients affected by chronic HS. This complication of HS is much more frequent than assumed. In fact, in the literature, we have been able to identify over 100 cases of HS patients developing SCC and the trend is on the rise.

Several authors have speculated on the pathogenic mechanisms leading to the development of SCC in HS affected areas. HPV infection has been supposed to have a role in the causation of SCC in patients with anogenital HS [2,3]. However, some authors have been unable to detect HPV DNA (genotypes 6, 11, 16, 18 and 33) using PCR, which suggests that HPV infection has a limited role in the process that leads to the development of SCC in HS affected areas [4]. Longstanding inflammation has also been suspected of promoting the development of SCC, with the release of some cytokines, such as TNF-alpha [5].

In contrast with this thesis, one must consider that TNF-alpha has an anticancer activity [6] and anti-TNF-alpha drugs may increase the risk of developing a SCC [7,8]. In our opinion, the concept of immunocompromised district (ICD) may well be the key for the comprehension of the pathogenic

mechanisms leading to the development of SCC in chronic HS.

The ICD is a novel concept, delineated by Ruocco et al. [9,10] that applies to an area of diseased or injured skin where local immune control has been altered, thereby permitting the development of a dysimmune reaction, infection, or tumour confined to the diseased or injured site. The skin is an active immune organ where a pool of immune-competent cells and cytokines co-ordinately act to create and maintain a balanced immune microenvironment [11].

The crucial role played by lymph drainage in regulating skin immunity is supported to by the fact that lymph stasis, whatever the cause, may give birth to skin regions with a dysregulation of the immune control and the origin of post-mastectomy Stewart-Treves angiosarcoma is a prototypical example of this condition [12]. In this light, the outbreak of SCC in long-standing HS could be considered a typical condition of an immunocompromised district. In detail, we suggest that the outbreak of SCC in long-standing HS may well be explained by the loco-regional immune default depending on the hindered traffic of immunocompetent cells in the lymphedematous area. In fact, anogenital lymphedema due to chronic, recurrent episodes of inflammation and scarring occurring in patients with HS and causing the blockade/destruction of lymph drainage routes, has long been noted to be a common sequela of HS [13–15].

A subclinical condition of lymphedema occurs in all patients with HS in the perineal or buttock areas. In most cases lymphedema cannot be diagnosed until tissue swelling is clinically visible, but, according to the International Society of Lymphology, a 'stage 0 lymphedema' does exist [16,17]. At the beginning, only physiologic changes (increased protein content) with no measurable fluid accumulation occur in the body region which is a candidate for lymphedema. Fluid accumulation supervenes later, and only then the clinician makes the diagnosis of lymphedema. In advanced stages, fibrotic changes and lipid deposition due to stasis of protein-rich extracellular fluid appear, resulting in an overt and difficult to manage condition. Interestingly, a recent study has focused on the role of subclinical lymphedema in the origin of both benign and malignant neoplasia [18].

The concept of ICD in dermatology throws new light on the pathogenesis of cancers, and may possibly pave the way for new therapeutic strategies. The crucial role of cancer prevention in dermatology, as well as in other branches of medicine, is so well known that it requires only a few comments. Knowing how vulnerable a diseased or injured skin site may be for an entire lifespan should alert both the physician and the patient to keep the site under special observation. Any new lesion appearing on that site should promptly be investigated by all means and, when necessary, immediately removed [10,19].

Disclosure statement


No potential conflict of interest was reported by the authors.

References

- [1] Zhang LQ, Tan C. Squamous cell carcinoma arising in chronic hidradenitis suppurativa: a lethal complication to be avoided. *Acta Oncol.* 2017;56:497–498.
- [2] Cosman BC, O'grady TC, Pekarske S. Verrucous carcinoma arising in hidradenitis suppurativa. *Int J Colorectal Dis.* 2000;15:342–344.
- [3] Lavogiez C, Delaporte E, Darras-Vercambre S, et al. Clinicopathological study of 13 cases of squamous cell carcinoma complicating hidradenitis suppurativa. *Dermatology (Basel).* 2010;220:147–153.
- [4] Hessam S, Sand M, Bechara FG. When inflammation shifts to malignancy: extensive squamous cell carcinoma in a female hidradenitis suppurativa/acne inversa patient. *J Dtsch Dermatol Ges.* 2017;15:86–88.
- [5] Kundu JK, Surh YJ. Inflammation: gearing the journey to cancer. *Mutat Res.* 2008;659:15–30.
- [6] Turculeanu A, Mogoantă CA, Ioniță E, et al. TNF- α evaluation in tonsil cancer. *Rom J Morphol Embryol.* 2015;56:101–106.
- [7] Zitelli KB, Zedek D, Ranganathan P, et al. Squamous cell carcinoma of the lip associated with adalimumab therapy for ankylosing spondylitis: a case report and review of TNF- α inhibitors and cutaneous carcinoma risk. *Cutis.* 2013;92:35–39.
- [8] Scheinfeld N. A case of a patient with stage III familial hidradenitis suppurativa treated with 3 courses of infliximab and died of metastatic squamous cell carcinoma. *Dermatol Online J.* 2014;20:3.
- [9] Ruocco V, Brunetti G, Puca RV, et al. The immunocompromised district: a unifying concept for lymphoedematous, herpes-infected and otherwise damaged sites. *J Eur Acad Dermatol Venereol.* 2009;23:1364–1373.
- [10] Ruocco V, Ruocco E, Piccolo V, et al. The immunocompromised district in dermatology: a unifying pathogenic view of the regional immune dysregulation. *Clin Dermatol.* 2014;32:569–576.
- [11] Baroni A, Buommino E, De Gregorio V, et al. Structure and function of the epidermis related to barrier properties. *Clin Dermatol.* 2012;30:257–262.
- [12] Ruocco V, Schwartz RA, Ruocco E. Lymphedema: an immunologically vulnerable site for development of neoplasms. *J Am Acad Dermatol.* 2002;47:124–127.
- [13] Faye O, Petit F, Poli F, et al. Lymphedema as a complication of hidradenitis suppurativa in three patients. *Ann Dermatol Venereol.* 2007;134:567–569.
- [14] Moosbrugger EA, Mutasim DF. Hidradenitis suppurativa complicated by severe lymphedema and lymphangiectasias. *J Am Acad Dermatol.* 2011;64:1223–1224.
- [15] Menter A. Recognizing and managing comorbidities and complications in hidradenitis suppurativa. *Semin Cutan Med Surg.* 2014;33:554–556.
- [16] International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema. Consensus document of the International Society of Lymphology. *Lymphology.* 2003;36:84–91.
- [17] International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema. 2009 Consensus document of the International Society of Lymphology. *Lymphology.* 2009;42:51–60.
- [18] Carlson JA. Lymphedema and subclinical lymphostasis (microlymphedema) facilitate cutaneous infections, inflammatory dermatoses, and neoplasia: a locus minoris resistentiae. *Clin Dermatol.* 2014;32:599–615.
- [19] Piccolo V, Baroni A, Russo T, et al. Ruocco's immunocompromised cutaneous district. *Int J Dermatol.* 2016;55:135–141.

LETTER TO THE EDITOR

Decitabine treatment of multiple extramedullary acute myeloid leukemia involvements after essential thrombocytemia transformation

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Progression of Philadelphia-negative myeloproliferative neoplasm (MPN) to acute myeloid leukemia (AML) is usually associated with a dismal prognosis [1]. Indeed, currently available treatment options for these patients are mostly