Title
A case of a patient with stage III familial hidradenitis suppurativa treated with 3 courses of infliximab and died of metastatic squamous cell carcinoma.

Journal
Dermatology Online Journal, 20(3)

Author
Scheinfeld, Noah

Publication Date
2014

DOI
10.5070/D3203021764

Volume 20 Number 3
March 2014

Letter

A case of a patient with stage III familial hidradenitis suppurativa treated with 3 courses of infliximab and died of metastatic squamous cell carcinoma.

Noah Scheinfeld

Dermatology Online Journal 20 (3): 17

Assistant Clinical Professor of Dermatology Weil Cornell Medical College

Correspondence:

Noah Scheinfeld
150 West 55th Street
New York NY 10019
Scheinfeld@earthlink.net

Abstract

Although rare, severe hidradenitis suppurativa (HS) of the anal, perianal, gluteal, thigh, and groin regions can evolve into squamous cell carcinoma (SCC). This usually does not occur until the HS has been present for more than 20 years. Malignant degeneration of HS in the axilla has not been reported. SCC has developed in dissecting cellulitis, acne conglobata, and pilonidal cysts (other members of the follicular tetrad). Whereas the male to female ratio of HS is 1:3, SCC in HS has a male to female ration of 5:1. The reasons behind malignant degeneration in HS are complex and might differ from the malignant degeneration causing Marjolin ulcers. It likely involves the presence of human papilloma virus (HPV) in affected areas (a rarity in the axilla), and impaired defensins, which combat HPV, in the skin of Hurley Stage III HS. In familial HS, the odds of developing SCC are likely greater because of independent loss-of-function mutations in the γ-secretase multiprotein complex, which regulates the Notch signaling pathway. Compromise of the Notch signaling pathway can undermine immune function and increase the risk of neoplastic development. Coincident SCC with use of tumor necrosis factor α blockers has been reported. I report a patient with long standing Hurley Stage III, familial HS, wwho developed metastatic SCC after 3 courses of infliximab and expired 11 months after the infliximab was started.

A 47-year-old male presented with progressive HS since early adulthood. His stage III hidradenitis suppurativa (HS) involved his groin, legs buttocks, and perineal areas. Interestingly, his HS was familial; one daughter also suffered from HS. A pilonidal cyst had been excised in the past. He suffered from hypertension for which he took ramipril, 2.5 mg per day. He did not admit to smoking. He had undergone numerous surgeries and courses of clindamycin with rifampin and clindamycin with minocycline. He used pregablin among other stronger medications for pain control. He had also taken isotretinoin years before without substantial long-term benefit. The various treatments were palliative but the HS always returned. He expressed that the pain from his HS was not bearable. He decided in consultations with his doctors to try infliximab owing to the positive clinical data for its efficacy in HS. He took 3 courses of infliximab 500mg, each of which was followed by surgical debridement of the perineal and anal areas. At the 3rd surgical debridement his physician noted the presence of squamous cell carcinoma (SCC) on July 28, 2008. The infliximab was stopped. However, the patient developed the patient underwent scanning soon after that showed soon after that the SCC had metastasized. He expired in June of 2009.

Discussion

Cancer and the follicular occlusion tetrad

All members of the follicular occlusion tetrad: dissecting cellulitis (DC) [1], acne conglobata(AC) [2,3], hidradenitis suppurativa(HS) [4], and pilonidal cysts(PC) [5] can exhibit involved sites with evolution into squamous cell carcinoma. DC, which is likely the rarest member of the tetrad of four has only one report of degeneration into SCC,;AC has two reports; pilonidal cysts and HS have many reports of SCC developing. A 2011 report [4] noted 64 cases of SCC arising in HS; more reports have been published since that time.

As dermatologists we are familiar with the concept that skin subject to chronic inflammation can develop squamous cell cancers called Marjolin's ulcers (often arising in burn patients) [6]. It is unclear if Marjolin's ulcer, which seems to arise most commonly on the leg, can provide us with data to understand why HS evolves into SCC because the inflammation involved in the two is different. Other areas of chronic inflammation, such as fistulas and chronic inflammation of Crohn disease can evolve into squamous cell carcinoma [7]. Several cases have noted Marjolin's ulcers arising in HS, but it is not clear whether it is simply HS degenerating into SCC or a true Marjolin's ulcer [8]. The development of cancer in HS and MU appear different; MU may require a certain kind of tissue damage to start the skin on its march to malignant degeneration. HS, on the other hand, likely needs more than simple inflammation to transform into SCC as I will try and demonstrate

In the 2011 review by Nunes [4], it is interesting to note that the number of cases of SCC arising in HS differ among sites. Of 64 patients with HS who developed SCC, the gluteal area was involved in 25 of 64 patients (39%), the perianal area in 20 (31%), the perineal area in 14 (22%), the thigh in seven (11%), the groin in one, and the trunk in one (2%); no SCCs were noted in the axilla. Another similar study only noted HS complicated by SCC in the groin, anal, perianal, and buttocks areas [9]. On the same note, although skin tags are common in the axilla, warts are not. Only one case of a wart arising in the axilla, which arose on an axillary skin tag was noted in the literature [10]. Skin tag are extremely common in the axilla while warts are not, scalp wart occur but are less common then genital warts explaining perhaps why a case of DC turned into an SCC.

This leads us to ask if the presence of human papilloma virus (HPV) combined with the defective cutaneous cellular immunity and chronic inflammation of HS are synergistic in the promotion of SCC in the groin, anus, and perianal areas.

Furthermore, one epidemiological study noted that women are more likely to develop HS and are more likely to have axillary and upper anterior torso involvement, whereas men are more likely to have perineal or perianal disease. The ratio of females to males of having HS is likely about 3:1.[11] The male:female ratio of SCC arising in HS was 5:1[4].

In addition, in one study found that 54.9% (140/255) of HS patients smoke; HS patients also smoke more than case controls, which also might make more them susceptible SCC development [11].

Observations on SCC arising in HS [4]

Long-standing disease affecting large anatomic areas and treated with multiple minor surgical interventions performed over many months or years
The male:female ratio was 5:1.
SCC does not seem to arise in HS of the axilla
Duration of HS before the cancer was diagnosed ranged from 2 to 50 years and predominantly from 20 to 30 years.
The size of the neoplastic region varied from 2.5 to 25 cm in diameter and in many patients it was reported as "large."
SCC occurs in Hurley Stage II or even more likely Hurley Stage III HS.

I would like to theorize that the combination of HS and presence of human papilloma virus (HPV) underlies, in part, the development of SCC in HS. Lavogiez et al [9] examined 217 patients with HS between 1993 and 2008 and found 10 cases of SCC, He detected HPV DNA using two highly sensitive and specific recently developed assays using a specific multiplex PCR combined with DNA microarray primer extension. The assays were combined in a single chip in order to detect 19 mucosal high-risk and potential high-risk HPV types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73 and 82) and 25 cutaneous HPV types from genus β (5, 8, 9, 12, 14, 15, 17, 19, 20, 21, 22, 23, 24, 25, 36, 37, 47, 49, 75, 76, 80, 92, 93 and 96). Lavogiez et al slightly modified the testing, with respect to the previous version, replacing the PCR forward primer for HPV-16 E7. In addition new oligonucleotides were added to the chip in order to detect 15 α-HPV low-risk (6, 11, 34, 40, 42, 43, 44, 54,

55, 57, 61, 67, 71, 72, 74, 81, 83 and 84) and 6 γ-HPV types (4, 48, 50, 60, 65 and 95). Overall this last version of the chip was able to detect 68 HPV types in addition to the β-globin. For each sample, 3 multiplex PCR reactions were performed for the amplification of the α-HPV high-risk types, the β-HPV types, and the α-HPV low-risk/γ-HPV types. The PCR reactions were performed with the QIAGEN Multiplex PCR kit according to the manufacturer's instructions. In this way, Lavogiez et al [9] investigated the presence of HPV in 8 genitoanal tumoral samples. With PCR, HPV was present in all cases: α-HPV with low-risk types (HPV-6), α-HPV with high-risk types (HPV-16 and HPV-68), and β-HPV (HPV types 17, 22, 23, 38, 76 and 80) were noted in 2, 8, and 7 cases, respectively. HPV-16 was demonstrated in 7 cases among 8. Thus it seems that the combination of the chronic inflammation and HPV impacts on the potential for malignant degeneration in HS.

I think there are several more pieces to the puzzle of why SCC develops in HS. The skin of stage III HS lacks defensins [12] and other anti-pathogenic peptides, which are important in fighting HPV[13]. Hoffman et al [12] studied 36 patients with HS and 57 healthy control subjects and showed that human β-defensin-3 expression is induced in lesional HS skin on transcriptional and protein levels. However, this up-regulation was not detectable in patients with severe HS (Hurley grade III). In contrast, messenger RNA expression of ribonuclease 7 was significantly diminished in lesional HS skin specimens irrespective of HS severity. Deficient constitutive production of ribonuclease 7 and, in severe HS, reduced human β-defensin-3 induction may contribute to impaired immunity within the hair follicle and thereby boost HS inflammation and severity.

Similarly, Dréno et al [13] noted that innate immunity markers (toll-like receptors 2, 3, 4, 7, and 9; intercellular adhesion molecule 1; interleukin [IL] 6 and 10; tumor necrosis factor; α melanocyte stimulating hormone; transforming growth factor β; β-defensin 2) showed abnormal expression. Dréno et al observed significantly decreased expression ($P < .001$) of all the innate immunity markers studied except IL-10 in nonlesional and lesional HS skin. The downregulation of innate markers was significantly stronger in lesional HS skin compared with normal skin, except for tumor necrosis factor.

Defensins are important in keeping HPV in check. Humans express two types of defensins, α- and β-defensins [14], which have antiviral activity against both enveloped and non-enveloped viruses. The diversity of defensin-sensitive viral species reflects a multitude of antiviral mechanisms. These include direct defensin targeting of viral envelopes, glycoproteins, and capsids. In addition, inhibition of viral fusion and post-entry neutralization are defensin functions. Binding and modulation of host cell surface receptors and disruption of intracellular signaling by defensins can also inhibit viral replication. In addition, defensins can function as chemokines to augment and alter adaptive immune responses, revealing an indirect antiviral mechanism. Copy number variation of the antimicrobial-gene, defensin beta 4, is associated with susceptibility to cervical cancer [15].

Wang [16] showed in familial HS independent loss-of-function mutations in *PSENEN*, *PSEN1* and *NCSTN*, the genes encoding essential components of the γ-secretase multiprotein complex. γ-Secretase is a transmembrane protease composed of four essential protein subunits: one catalytic presenilin (PSEN1) subunit, and three cofactor subunits, presenilin enhancer 2 (PSENEN), nicastrin (NCSTN) and anterior pharynx defective 1 (APH1). Recently, the pathogenic role of NCSTN and PSENEN mutations in familial HS has been confirmed.[17] γ-Secretase is involved in the regulation of the canonical Notch signalling pathway. Intramembrane cleavage of Notch by γ-secretase releases the intracellular domain of Notch (NICD) that exhibits signaling activity in the nucleus Impaired NOTCH signaling also inhibits the generation of natural killer cells and causes an insufficient response of the innate immune system once it is activated, resulting in a compromised defense mechanism and prolonged inflammatory activity [18]. This might be another factor in the development of SCC in severe cares of HS. Frequently, familial HS is more severe than sporadic HS [19]. Notch signaling plays a role in tumor suppression of head and neck cancers [20].

It remains controversial if and to what extent infliximab promotes the development of squamous cell cancer, in particular with short-term use [21]. It is possible that infliximab undermines and inflammatory response and DNA repair [22]. It is possible that the patient in this case might have had SCC independent of infliximab use because his HS was long standing, severe and familial. Rahman et al [23] noted 2 cases of oral SCC in patients who had used TNFAB but concluded that "currently there is no clear cut cause and effect relationship between the administration of a TNF antagonist and the onset of oral SCC. However, from our 2 reports, a tenuous link may be proposed. Temporality of infliximab use does not mean causality when as SCC develops [24]. Still it must be noted that SCCs have developed in patients treated with infliximab,[25] sometimes rapidly [26].

In conclusion, I note a case of a patient with familial stage III HS who was noted to have SCC soon after starting infliximab. Medical treatment is changing for both warts and for HS. For warts, the use of vaccines against HPV 6, 11, 16 and 18 will change the epidemiology of oncogenic HPV strains in the future. The vaccination is relativity new but it is already decreasing HPV infection in Europe where it was first deployed and will do so in the United States in the years to come. For HS patients the use of tumor necrosis factor alpha-blockers, which are immunosuppressive, might adversely affect the incidence of SCC in those who are prone to SCC owing to alteration of the NOTCH gene products and decreased defensins. Sorting out the factors involved in this patient's development of metastatic SCC is a complex task, but the case is important to note.

References

1. Curry SS, Gaither DH, King LE Jr. Squamous cell carcinoma arising in dissecting perifolliculitis of the scalp, A case report and review of secondary squamous cell carcinomas. J Am Acad Dermatol.1981;6:673-8.
2. Quintal D, Jackson R. Aggressive squamous cell carcinoma arising in familial acne conglobata. J Am Acad Dermatol. 1986 Feb;14(2 Pt 1):207-14. [PMID: 2936774]
3. Camisa C. Squamous cell carcinoma arising in acne conglobata. Cutis. 1984 Feb;33(2):185-7, 190. [PMID: 6230214]
4. Nunes LF, de Castro Neto AK, Vasconcelos RA, Cajaraville F, Castilho J, Rezende JF, Noguera WS. Carcinomatous degeneration of pilonidal cyst with sacrum destruction and invasion of the rectum. An Bras Dermatol. 2013 Nov-Dec;88(6 Suppl 1):59-62. [PMID: 24346881]
5. Losanoff JE, Sochaki P, Khoury N, Levi E, Salwen WA, Basson MD. Squamous cell carcinoma complicating chronic suppurative hydradenitis. Am Surg. 2011 Nov;77(11):1449-53. [PMID: 22196655]
6. Yu N, Long X, Lujan-Hernandez JR, Hassan KZ, Bai M, Wang Y, Wang X, Zhao R. Marjolin's ulcer: a preventable malignancy arising from scars. World J Surg Oncol. 2013 Dec 17;11(1):313. [PMID: 24341890]
7. The relationship between fistulas in Crohn's disease and associated carcinoma. Report of four cases and review of the literature. Church JM, Weakley FL, Fazio VW, Sebek BA, Achkar E, Carwell M. Dis Colon Rectum. 1985 May;28(5):361-6. [PMID: 3158499]
8. Lin MT, Breiner M, Fredricks S. Marjolin's ulcer occurring in hidradenitis suppurativa. Plast Reconstr Surg. 1999 Apr;103(5):1541-3. [PMID: 10190470]
9. Lavogiez C, Delaporte E, Darras-Vercambre S, Martin De Lassalle E, Castillo C, Mirabel X, Laurent F, Patenotre P, Gheit T, Talmant JC, Beylot-Barry M, Martinot V, Piette F, Aubin F, Mortier L. Clinicopathological study of 13 cases of squamous cell carcinoma complicating hidradenitis suppurativa. Dermatology. 2010;220(2):147-53. [PMID: 20029163]
10. 10. Verma SB. Verruca plus acrochordon: an 'over the top' skin tag. Clin Exp Dermatol. 2009 Oct;34(7):e432-3. [PMID: 19747304]
11. Vazquez BG, Alikhan A, Weaver AL, Wetter DA, Davis MD. Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota. J Invest Dermatol. 2013 Jan;133(1):97-103. [PMID: 22931916]
12. Hofmann SC, Saborowski V, Lange S, Kern WV, Bruckner-Tuderman L, Rieg S. Expression of innate defense antimicrobial peptides in hidradenitis suppurativa. J Am Acad Dermatol. 2012 Jun;66(6):966-74. [PMID: 21982063]
13. Dréno B, Khammari A, Brocard A, Moyse D, Blouin E, Guillet G, Léonard F, Knol AC. Hidradenitis suppurativa: the role of deficient cutaneous innate immunity. Arch Dermatol. 2012 Feb;148(2):182-6. [PMID: 22004878]
14. Wilson SS, Wiens ME, Smith JG Antiviral mechanisms of human defensins. J Mol Biol. 2013 Dec 13;425(24):4965-80. [PMID: 24095897]
15. Abe S, Miura K, Kinoshita A, Mishima H, Miura S, Yamasaki K, Hasegawa Y, Higashijima A, Jo O, Sasaki K, Yoshida A, Yoshiura K, Masuzaki H. Copy number variation of the antimicrobial-gene, defensin beta 4, is associated with susceptibility to cervical cancer. J Hum Genet. 2013 May;58(5):250-3. [PMID: 23466823]
16. Wang B, Yang W, Wen W, Sun J, Su B, Liu B, Ma D, Lv D, Wen Y, Qu T, Chen M, Sun M, Shen Y, Zhang X.Gamma-secretase gene mutations in familial acne inversa. Science. 2010 Nov 19;330(6007):1065. [PMID: 20929727]
17. Melnik BC, Plewig G.Impaired Notch signalling: the unifying mechanism explaining the pathogenesis of hidradenitis suppurativa (acne inversa). Br J Dermatol. 2013 Apr;168(4):876-8. [PMID: 23020871]
18. Melnik BC, Plewig G. Impaired Notch-MKP-1 signalling in hidradenitis suppurativa: an approach to pathogenesis by evidence from translational biology. Exp Dermatol 2013;22:172-77.
19. Chandramohan K, Mathews A, Kurian A, Thomas S, Ramachandran K. Squamous cell carcinoma arising from perineal lesion in a familial case of Hidradenitis suppurativa. Int Wound J. 2009 Apr;6(2):141-4. [PMID: 19432663]
20. 20. Rothenberg SM, Ellisen LW. The molecular pathogenesis of head and neck squamous cell carcinoma. J Clin Invest. 2012 Jun 1;122(6):1951-7. [PMID: 22833868]
21. O'Donnell S, Murphy S, Anwar MM, O'Sullivan M, Breslin N, O'Connor HJ, Ryan BM, O'Morain CA. Safety of infliximab in 10 years of clinical practice. Eur J Gastroenterol Hepatol. 2011 Jul;23(7):603-6. [PMID: 21602689]
22. Faurschou A. Role of tumor necrosis factor-α in the regulation of keratinocyte cell cycle and DNA repair after ultraviolet-B radiation. Dan Med Bull. 2010 Oct;57(10):B4179. [PMID: 21040686]
23. Rahman N, Healy C, Flint SR, Stassen LF. Cautionary note: a possible association between oral squamous cell carcinoma and tumor necrosis factor antagonists; need for oral screening. J Clin Rheumatol. 2010 Jun;16(4):197-9. [PMID: 20511984]
24. Engel SH, Hullar TE, Adkins DR, Thorstad WL, Sunwoo JB. Temporal relationship between antitumor necrosis factor-alpha antibody therapy and recrudescence of head and neck squamous cell carcinoma. Laryngoscope. 2008 Mar;118(3):450-2. [PMID: 18090867]
25. Maalouf E, Faye O, Poli F, Cosnes A, Revuz J. Fatal epidermoid carcinoma in hidradenitis suppurativa following treatment with infliximab. Ann Dermatol Venereol. 2006 May;133(5 Pt 1):473-4. [PMID: 16760840]
26. Esser AC, Abril A, Fayne S, Doyle JA. Acute development of multiple keratoacanthomas and squamous cell carcinomas after treatment with infliximab. J Am Acad Dermatol. 2004 May;50(5 Suppl):S75-7. [PMID: 15097933]