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Case of a squamous cell carcinoma associated with a subcutaneous foreign body

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Nonmelanoma skin cancer, consisting of squamous and basal cell carcinoma, is the most common malignancy in the United States. The most common risk factor is exposure to ultraviolet radiation; however, these malignancies have also developed at sites of exposure to industrial agents, ionizing radiation, and areas of chronic inflammation. This case details an 85-year-old white male who presented with a squamous cell carcinoma that developed proximate to a subcutaneous metallic foreign body. The lesion was successfully excised with negative margins. We review the literature and discuss potential mechanisms of foreign body carcinogenesis.

There are more than two million cases of nonmelanoma skin cancer (NMSC) reported in the United States each year, making it the most common malignancy in this country.[1] The most important risk factor for NMSC, usually squamous cell carcinoma (SCC) or basal cell carcinoma (BCC), is exposure to solar ultraviolet (UV) radiation. However, there are a variety of other risk factors for NMSC including industrial exposure to oils and tar, chronic ulcers, draining osteomyelitis, burn scars, and ionizing radiation.[2] In addition, NMSC of the oral cavity has been associated with tobacco use and betel nut chewing.[2]

Chronic irritation has long been associated with the development of malignancy. In 1828, Jean Nicolas Marjolin was the first to describe tumors arising from sites of previous trauma.[3] The term *Marjolin's ulcer* is traditionally associated with malignancy arising from burn scars.[4] However, clinical reports suggest that malignancy can arise from unstable scars or sites of inflammation caused by numerous clinical entities, including venous stasis, frostbite, sites of vaccination or skin grafting, chronic pressure ulceration, discoid lupus erythematosus, hidradenitis suppurativa, pilonidal abscess, acne conglobata, amputation stumps and sites of infection from syphilis, lymphogranuloma venereum, or leshmaniasis.[4-6] Consequently, Marjolin's ulcer is now accepted to be a SCC, or more rarely a BCC, that arises at a site of chronic inflammation or a nonhealing wound.[4-6]

In their case report and accompanying literature review, Rieger et al.[4] describe the development of a BCC at the site of retained grenade fragments; this was the sixth reported case of malignancy developing after grenade injury. Other reports describe the development of malignancy at sites of chronic irritation resulting from the presence of a foreign body, such as that associated with a poorly fitting ocular prosthesis,[7] an air gun pellet retained in the maxillary sinus,[8] and an intrauterine device (IUD) that migrated from the uterus to the bladder.[9]

Report of case

An 85-year-old white, male, retired farmer with a 35 pack-year history of tobacco use presented to his primary care

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provider for evaluation of a lesion of uncertain behavior on the right posterior aspect of his neck. The patient initially thought the lesion was an "ingrown hair" but decided to seek treatment after he was not able to express material from it and because the lesion had been increasing in size over the course of one month. The lesion was not painful, did not itch or cause any other discomfort, and did not bleed unless irritated.

The patient's previous medical history was most notable for prostate carcinoma successfully treated with localized radiation. In addition, the patient also had a history consistent with cardiomyopathy, congestive heart failure, coronary artery disease, hypertension, dyslipidemia, left ventricular thrombosis, lumbar canal stenosis, chronic renal insufficiency, gout, reliance on a walker for ambulation, tinea cruris, peptic ulcer disease, hemorrhoids, olecranon bursitis, and vertigo. Previous surgical history was significant for coronary artery bypass grafting, implantation of a defibrillator, cholecystectomy, cataract surgery, inguinal herniorrhaphy, bilateral total hip arthroplasty, and venous ligation.

Vital signs recorded in the clinic were blood pressure 110/60 mm Hg, heart rate 80 beats/min, respiration rate 12 breaths/min, temperature 97.8°F, height 69 inches, weight 190.6 lbs, body mass index 28.1 kg/m^2.

General examination revealed an elderly male in no apparent distress. Auscultation of the chest revealed a heart with regular rate and rhythm and without murmur; the lungs were clear to auscultation bilaterally. Examination of the integument was remarkable for an 8 × 7-mm scaly, verrucoid, nodular lesion that was pearly pink in color at its base with an amber-colored central keratinaceous projection. There was no erythema, warmth, or telangiectasia associated with the lesion. Laboratory testing obtained in a recent routine office visit was notable for an elevated serum creatinine, elevated blood glucose level, and hypertriglyceridemia; this was consistent with the patient's previous medical history. A complete list of laboratory values is shown in Table 1.

Table 1 Laboratory values

Lab	Result	Reference range
White blood cell count	7.4 K/μL	4.5-11.0 K/μL
Hemoglobin	14.1 g/dL	13.0-18.0 g/dL
Hematocrit	41.00%	39.0-52.0%
Platelets	177 K/μL	150-450 K/μL
Sodium	142 mmol/L	136-145 mmol/L
Potassium	4.4 mmol/L	3.5-5.1 mmol/L
Chloride	103 mmol/L	98-107 mmol/L
Carbon dioxide	28 mmol/L	23-32 mmol/L
Glucose	107 mg/dL	70-100 mg/dL
Blood urea nitrogen	19 mg/dL	7-25 mg/dL
Creatinine	1.5 mg/dL	0.6-1.3 mg/dL
Calcium	9.1 mg/dL	8.5-10.5 mg/dL
Aspartate aminotransferase	27 U/L	30-65 U/L
Alanine aminotransferase	34 U/L	30-175 U/L
Total cholesterol	125 mg/dL	105-200 mg/dL
High-density lipoprotein cholesterol	21 mg/dL	32-96 mg/dL
Trigylcerides	478 mg/dL	30-175 mg/dL

Differential diagnosis

Any dermatologic condition presenting as a scaly nodule could theoretically be entertained in the differential diagnosis; however, the most likely diagnoses consistent with the physical appearance of this asymptomatic skin lesion presenting on the neck of an elderly retired farmer included a SCC or BCC, keratoacanthoma, or cutaneous horn. Other diagnostic possibilities considered were a cutaneous xanthoma or verruca vulgaris.

The most probable diagnosis in the differential was BCC or SCC because a suspicious lesion presenting on the posterior neck of a farmer would have high cumulative exposure to UV radiation, the largest risk factor for NMSC. Invasive SCC often presents as a nodule when it is well-differentiated and can erupt over the course of weeks.[10] Similarly, there is a nodular variant of BCC that can be difficult to distinguish from SCC. The lesion in this patient had a central keratinaceous projection not uncommon in SCC and often undistinguishable from keratoacanthoma, another clinical entity in the differential.[10] Keratoacanthomas, which typically occur on sun-exposed areas, are a variant of SCC that present as a nodule with a keratotic plug at their center; the treatment is excision.[10] Similarly, the presence of the keratinaceous projection in this lesion was consistent with a cutaneous horn, which presents with the appearance of an animal horn arising from a nodular base. Often, the nodular base has histological evidence of actinic keratosis, or invasive or in situ SCC. For this reason, a cutaneous horn should be excised.[10] The patient's history of hypertriglyceridemia caused us to consider xanthomas in our differential. Xanthomas present as yellow, brown, pink, or orange plaques or nodules, and histological analysis reveals macrophages laden with lipids.[10] The scaly, hyperkeratotic nature of this lesion also caused us to consider verruca vulgaris, the common wart. This entity occurs when human papillomavirus (HPV) infects the skin, resulting in hyperkeratosis.

The history and physical examination allowed the differential diagnosis to be refined, although the final diagnosis remained uncertain. Because the differential included SCC, a malignancy with the potential for metastasis, and keratoacanthoma, which often has SCC at its base, we recommended an excisional biopsy for microscopic diagnosis.

Clinical course

The patient elected to undergo excisional biopsy and informed consent was obtained. The base of the lesion was

anesthetized using a solution of lidocaine with 1% epinephrine and then excised with minimal bleeding as an ellipse with a long axis of 27 mm, a short axis of 16 mm, and a depth of 6 mm. The wound was closed with six simple interrupted sutures of 5.0 nylon and the area was cleansed with sterile saline. Antibiotic ointment and a sterile dressing were then applied. The excised specimen was sent for pathologic analysis. The patient returned for a wound check four days post-procedure and sutures were removed six days after that.

During the procedure, a 2-mm spherical metallic fragment was discovered in the subcutaneous tissue closely associated with the lesion being excised. Unfortunately, during transfer of the metallic fragment to a specimen container, it was dropped and not able to be recovered. For this reason, the exact chemical composition of the fragment remains unknown; however, all personnel present during the procedure were able to examine the fragment and agreed it was metallic.

The patient does not recall a specific incident explaining the presence of this metallic foreign body. Upon further questioning, the patient denied a history of military involvement or a history of shrapnel. However, the patient does have a history of occasional hunting as recently as 25 years ago and received a BB gun at 8 years of age. Either of these elements in the patient's history may explain the presence of this metallic foreign body, although we are unable to definitively determine the source or timeline.

Pathologic examination revealed a well-differentiated SCC that was excised with free margins. There were numerous inflammatory cells present but the pathologist was unable to determine whether this was because of a foreign body reaction. The patient's medical conditions remain stable and there has been no adenopathy or recurrence of skin lesions noted during subsequent clinical encounters.

Discussion of case

There are at least five categories to which the cause of a cancer can be attributed: spontaneous errors in DNA replication, inflammatory or cytotoxic carcinogenic materials, materials that directly injure DNA, radiation exposure, and viral oncogenes.[11] In some parts of the world, up to one fourth of all deaths resulting from malignancy are attributed to infection or inflammation.[11] Foreign body carcinogenesis in humans appears to be related to the chronic inflammation that results.

One common theme among malignancy resulting from chronic irritation is a period of latency before development of a tumor. Authors have reported the lag period for tumor development at sites of chronic irritation, previous scar, or burn injury to be 15 to 35 years.[3-6] Similarly, tumor latency for foreign bodies implanted into humans is around 20 years.[11] However, there are examples of malignancy developing acutely, sometimes as soon as weeks to months after an initial injury.[4,5]

Foreign body carcinogenesis has been well studied in animal models. These investigations have shown tumorigenicity to be dependent on the size, shape, porosity, smoothness, and fibrous encapsulation of the foreign body.[12,13] Interestingly, development of tumor after introduction of foreign bodies into humans is rarer than the same phenomenon occurring in other animal species.[13] In fact, in humans, tumors induced by the presence of foreign bodies are quite rare.[4]

The cause of tumor conversion and progression at sites of chronic inflammation or at sites of exogenous foreign body implantation has been the subject of scientific inquiry. Simmons et al.[6] proposed that areas of chronic inflammation may be predisposed to developing malignancy because an increased rate of cell turnover would be expected to increase the risk for a spontaneous replication error in DNA during cell division. Although spontaneous replication error may be a causative factor in the development of some neoplasms, it is likely that another mechanism is at play in a foreign body-induced tumor.

Current investigations have focused on the complicity of neutrophils and macrophages in tumorigenesis at inflammatory foci.[11,14,15] Specifically, these investigators implicate the release of oxygen and nitrogen oxide free radicals from leukocytes because these reactive molecules exhibit cytotoxic and mutagenic effects. Molecular co-conspirators also have been identified. These tumor promoter molecules include tumor necrosis factor-alpha (TNF-α) and interleukin-1β. TNF-α is notable as an inducer of MMP9 release from macrophages; in turn, MMP9 promotes angiogenesis by activating vascular endothelial growth factor.[15] Despite these findings, much remains to be learned about foreign body tumorigenesis.

Conclusion

In this case, we describe an 85-year-old male presenting with a well-differentiated SCC that developed in close proximity to a subcutaneous foreign body. We believe there to be a latency period of 25 years or more from foreign body implantation to development of malignancy. We cannot exclude the possibility that the development of a SCC proximate to a subcutaneous foreign body in this patient is coincidental. As discussed, UV radiation exposure is the leading cause of NMSC; thus, NMSC on the neck of an elderly farmer is not an uncommon finding. However, the presence of a retained metal fragment as a possible precipitating factor in this case is noteworthy. Although there is not sufficient evidence to recommend for automatic excision of known subcutaneous foreign bodies, we suggest further research be done to ascertain their significance as precipitants of malignancy.

References

1. Wheless L, Black J, Alberg AJ: Nonmelanoma skin cancer and the risk of second primary cancers: a systematic review. Cancer Epidemiol Biomarkers Prev 19:1686-1695, 2010
2. Murphy GF, Sellheyer K, Mihm MC: The skin. In: Kumar V, Abbas AK, Fausto N, eds. *Robbins and Cotran: Pathologic basis of disease*, 7th ed. Philadelphia, PA: Saunders, 2005, pp 1227-1271
3. Fishman J, Parker M: Malignancy and chronic wounds: Marjolin's ulcer. J Burn Care Rehabil 12:218-223, 1991
4. Rieger UM, Kalbermatten DF, Wettstein R, et al: Marjolin's ulcer revisited—basal cell carcinoma arising from grenade fragments? Case report and review of the literature. J Plast Reconstr Aesthet Surg 61:65-70, 2008
5. Copcu E: Marjolin's ulcer: A preventable complication of burns? Plast Reconstr Surg 124:156e-164e, 2009
6. Simmons MA, Edwards JM, Nigam A: Marjolin's ulcer presenting in the neck. J Laryngol Otol 114:980-982, 2000
7. Endo T, Hata J, Togashi S, et al: Conjunctival squamous cell carcinoma of the orbit 40 years after enucleation. Ophthal Plast Reconstr Surg 22:299-301, 2006
8. Kühnel TV, Tudor C, Neukam FW, et al: Air gun pellet remaining in the maxillary sinus for 50 years: A relevant risk factor for the patient? Int J Oral Maxillofac Surg 39:407-411, 2010
9. Gökce MI, Süer E, Tangal S, et al: Squamous cell carcinoma of the bladder associated with chronic irritation related to a migrated intrauterine device. Scand J Urol Nephrol 44:183-185, 2010
10. Wolff K, Johnson RA: *Fitzpatrick's color atlas & synopsis of clinical dermatology*, 6th ed. New York: McGraw-Hill, 2009
11. Okada F: Beyond foreign-body induced carcinogenesis: impact of reactive oxygen species derived from inflammatory cells in tumorigenic conversion and tumor progression. Int J Cancer 121:2364-2372, 2007
12. Ferguson DJ: Cellular attachment to implanted foreign bodies in relation to tumorigenesis. Cancer Res 37:4367-4371, 1977
13. Moore GE: Foreign body carcinogenesis. Cancer 67:2731-2732, 1991
14. Kim HW, Murakami A, Williams MV, et al: Suppressive effects of selected antioxidants on the activated leukocytes-induced mutagenesis in the co-culture assay systems. Biosci Biotech Biochem 68:238-242, 2004
15. Moizhess TG: Carcinogenesis induced by foreign bodies. Biochemistry (Moscow) 73:763-775, 2008