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Skin Cancer (T Ito, Section Editor)

Diagnosis and Management of Basal Cell Carcinoma

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Opinion statement

Basal cell carcinomas (BCCs) are common skin cancers that tend to appear on sun-exposed skin. Pathobiologically, activation of the Hedgehog signaling pathway characterizes the majority of cases. In general, BCCs are slow-growing and rarely metastasize. Nevertheless, they are locally invasive and can be destructive. While typical cases are diagnosed based on clinical findings, the clinicopathological manifestations are varied. Consequently, skin biopsy is essential to confirm the diagnosis and evaluate the risk of recurrence. In the treatment of primary lesions, the initial goal is to complete tumor removal, whether by conventional surgical excision, Mohs micrographic surgery, cryosurgery, electrodesiccation and curettage, topical application of imiquimod or fluorouracil, photodynamic therapy, or radiation therapy. Of these treatments, surgical excision and Mohs surgery are the most commonly used because of their association with a low recurrence rate and the ability to confirm residual tumor pathologically. However, other treatment options may be preferred according to patient condition, tumor location, and risk of recurrence. In the treatment of metastatic or locally advanced lesions, smoothened inhibitors, which inhibit Hedgehog signaling pathway activation, were recently approved and impressive tumor shrinkage effects have been described. Although the exact prognosis of metastatic BCC has not been analyzed, it is probably poor due to the rarity of such condition. However, emerging molecular targeting agents hold therapeutic promise.

Introduction

Basal cell carcinomas (BCCs) are common skin cancers arising from the basal layer of the epidermis and adnexal structures. Clinically, BCCs tend to appear on sun-exposed skin, especially on the face and neck [1]. Most BCCs are slow growing and have a low metastatic potential. However, they are locally invasive and

can be destructive to surrounding tissues [2]. Several factors play important etiological roles in the development of BCC, among which exposure to the ultraviolet (UV) radiation in sunlight is the most critical environmental cause. In particular, individuals with fair skin, light-colored eyes, red hair, northern European ancestry, advanced age, freckling from childhood, and a personal history of frequent sunburns are at high risk of BCC associated with UV exposure [3, 4]. Long-term arsenic exposure due to the continuous ingestion of contaminated water, food, and medications [5–7], ionizing radiation for the treatment of skin diseases or childhood cancers [8, 9], immunosuppression due to human immunodeficiency virus infection, and a history of treatment with immunosuppressive agents are additional risk factors for BCC [10, 11].

Pathobiologically, activation of the Hedgehog (HH) signaling pathway underlies the majority of BCCs and serves as a therapeutic target [12–14]. Involvement of the HH pathway was first recognized following the identification of a germline mutation of the *patched homolog 1 (PTCH1)* gene in basal cell nevus syndrome, after which mutations in genes related to the HH signaling pathway, including *PTCH1* and *smoothened homolog (SMO)*, were identified in sporadic BCCs [14, 15]. In general, activation of HH signaling is initiated by the cell surface protein SMO, which is inhibited by another cell surface protein, PTCH1 [14]. Binding of the HH ligand to PTCH1 releases this inhibition and thereby activates the HH pathway. Mutations in *PTCH1* result in a loss of its inhibitory role, while mutations in *SMO* lead to constitutive signaling activation [16–18].

The incidence of BCCs varies depending on race and on geographic factors such as latitude and sun exposure [19]. The reported incidence rates per 100,000 person-years are highest in Australia (> 1000/100,000), lowest in Africans in Kenya (< 1/100,000), 76.21 in England, and 15–16.5 in Japan [19–22]. For Caucasian residents of the USA, population-based studies in Minnesota and Kauai, Hawaii, have estimated incidence rates of 146 and 422/100,000 person-years, respectively [23, 24]. However, the rates continue to increase worldwide. In USA, the age-adjusted incidence rates almost doubled from the late 1980s to the middle 2000s in both men and women [25].

As epidemiological and pathobiological information accumulates, healthcare workers need to update both the diagnostic approach to BCC and the methods used in its treatment.

Diagnosis

Basal cell carcinomas are diagnosed by direct inspection, dermoscopic examination, and histological examination. Typical lesions can be diagnosed by direct inspection based on those clinical findings. In addition, dermoscopic examination will improve the diagnostic accuracy of suspicious lesions [26, 27]. Nevertheless, a skin biopsy is essential to confirm the diagnosis and to estimate the risk of recurrence. Histopathologically, BCCs commonly consist of a proliferation of uniform, basaloid cells with a hyperchromatic nucleus and relatively little, poorly defined cytoplasm [28]. While the basaloid cells resemble epidermal basal cells morphologically, their behavior is similar to that of follicular germinative cells [29, 30].

The variable clinicopathological manifestations of BCC include nodular, superficial, fibroepithelial, morpheaform, and infiltrative BCC as well-defined subtypes with distinct clinicopathological findings. Other subtypes of histopathological importance are micronodular and basosquamous BCC, the presence of which will affect the therapeutic strategy and patient prognosis. Moreover, many tumors exhibit the histopathological findings of multiple subtypes in the same lesion [31].

Nodular type BCC

Between 60 and 80% of all BCCs are of the nodular type, which typically occur on the face and neck [32, 33]. The lesions usually present as a pearly or translucent papule or nodule with telangiectatic vessels. The lesion may often be described as having a "rolled" border, where the periphery of the lesion is raised compared to the middle. Ulceration may be present in larger lesions. Dermoscopic examination frequently reveals arborizing telangiectasias, translucency, and a milky red background [27, 34]. Histopathologically, nodular lesions consist of a proliferation of basaloid cells forming large tumor nests with peripheral palisading and a central haphazard arrangement. Retraction spaces between the tumor nests and surrounding stroma are commonly noted [28, 35].

Superficial type

Approximately 20% of all BCCs are of the superficial type, which typically occurring on the trunk and limbs [33]. The lesions vary in size, from a few millimeters to several centimeters in diameter and usually present as a well circumscribed, slightly scaly, light reddish patches or thin plaques. Additional features are central atrophy or a thin rolled border [33]. On dermoscopic examination, short fine telangiectasia, structure-less hypopigmentation, structure-less hyperpigmentation, multiple erosions, and a milky red background are common characteristics [27, 34]. Histopathological examination shows multiple small islands of basaloid cells attached to the undersurface of the epidermis and usually confined to the papillary dermis. A narrow zone of fibrous stroma may surround the nests [28, 35].

Morpheaform (sclerosing, desmoplastic) type

Between 5 and 10% of BCCs are of the morpheaform type, which are commonly found on the face and neck [32]. The flesh-colored infiltrated plaques have poorly defined borders resembling a scar or morphea-like plaque [33]. Dermoscopic examination frequently shows short, fine telangiectasia, structure-less hypopigmentation, and a white shiny area with a milky red background [34]. Histopathologically, a sclerotic collagenous stroma surrounds narrow elongated strands and small islands of tumor cells [28, 35].

Infiltrative type

The infiltrative type of BCC usually occurs in association with preexisting BCCs of other subtypes, especially the nodular type. Clinically, the lesions are whitish or pale pink, poorly defined, indurated, flat, or depressed plaques. Overlying crusts, erosions, ulcerations, and papules may also be present [33]. Histopathologically, the proliferation of basaloid cells forming tumor nests with a peripheral palisading pattern is noted superficially, and infiltrating nests with elongated strands of basaloid cells lacking a peripheral palisading pattern are noted on those periphery or base [28, 35].

Fibroepithelial type

This uncommon variant usually develops on the lower back. It presents as a skin-colored or erythematous soft papule or pedunculated papulonodular lesion resembling fibroma or papilloma [33]. Histopathologically,

fibroepithelial type BCC is composed of thin anastomosing strands of basaloid cells set in a prominent loose stroma. The tumor cells have a high proliferative index [28, 35].

Pigmented BCCs

Pigmented BCC is a generic term for BCCs having pigmented features, which may be found in all subtypes [36]. However, while pigmented lesions are frequently seen in Asians and Africans, they are rare in Caucasians. Nonetheless, on dermoscopic examination, almost 30% of BCCs clinically classified as "non-pigmented BCC" have pigmented structures [37]. The dermoscopic findings are closely associated with the histopathological features of the lesion, resulting in the recognition of two groups of lesions. In the first, structures representing pigmentation at the dermoepidermal junction which appear brown in color. Typical findings include maple leaf-like or spoke-wheel areas, in-focus dots, and concentric structures, all of which are characteristic of superficial and infiltrating BCC. In the second, structures representing pigmentation at the deeper layers of the dermis which appear blue or gray in color. These findings include multiple blue-gray ovoid nests and blue-gray globules, both of which are characteristic of nodular BCC [38]. In fact, spoke-wheel areas and multiple blue-gray globules are regarded as reliable diagnostic indicators of BCC [39].

Other histopathologically significant types

Micronodular type BCC is a histopathological variant that shares several histological features with nodular BCC, and the two frequently co-localize within the same lesion [31]. However, the tumor nests of the micronodular type are much smaller than those of the nodular type and peripheral palisading is not always as well developed. In addition, the clinical behavior of micronodular BCC may mimic that of the morpheaform type, and the tumors have a propensity for local recurrence [28, 35]. Basosquamous cell carcinoma is a rare subtype that behaves aggressively. While the definition and terminology are controversial, this subtype is currently considered to be BCC undergoing squamous differentiation. The three cell types seen in basosquamous cell carcinoma are basaloid cells, squamoid cells, and intermediate cells. Basaloid cells are slightly larger, paler, and rounder than the cells of nodular BCCs. Squamoid cells show a copious eosinophilic cytoplasm, and intermediate cells resemble those seen in metatypical tumors [28, 35].

Treatment

Risk classification of the primary lesion

As metastasis rarely occurs in BCC, appropriate treatment of the primary lesion results in a high probability of cure. While several established therapies are available for primary lesions, their use differs according to the risk of recurrence and the patient's condition. Thus, pretreatment assessment of the risk factors for recurrence is important in the choice of therapy. The NCCN guidelines define clinical and pathological risk factors for the recurrence of BCCs [40]. Clinical risk factors are immunosuppression, prior radiotherapy of the tumor lesion, a recurrent tumor, poor border clarity, a tumor of any size in high-risk areas (central face, eyelids, eyebrows, periorbital area, nose, lips, chin, mandible,

preauricular and postauricular skin, temple, ear, as well as the genitalia, hands, and feet), a tumor with a major axis ≥ 10 mm in medium-risk areas (cheeks, forehead, scalp, neck, and pretibia), and a tumor with a major axis ≥ 20 mm in low-risk areas (trunk and extremities, excluding the pretibia, hands, feet, nails, and ankles). Pathological risk factors are perineural involvement and a morpheaform, basosquamous, micronodular, or mixed infiltrative subtype.

Surgical excision

Surgical excision is the standard therapy for BCCs, as it is highly efficacious. Studies of the surgical margins likely to achieve the complete removal of tumors at various anatomical locations have reported > 95% 5-year cure rates with 4- to 5-mm surgical margins [41, 42]. In a meta-analysis of 89 studies in which 16,066 BCCs (excluding recurrent BCCs, morpheaform BCC, and BCCs on irradiated lesions) were analyzed, the complete excision rates were similar for tumors with surgical margins of 3–5 mm. The mean recurrence rates for tumors with surgical margins of 5, 4, 3, and 2 mm were 0.4, 1.6, 2.6, and 4.0%, respectively [43]. Based on these findings, a surgical margin of at least 4 mm is currently recommended by the guidelines of several dermatological and oncologic associations [40, 44–46]. However, these recommendations are based mainly on studies of non-pigmented BCCs in Caucasians whereas several retrospective studies have shown that pigmented BCCs can be resected with smaller surgical margins, as these lesions are relatively well-demarcated and their borders more easily evaluated than is the case for non-pigmented BCCs [47, 48].

Mohs micrographic surgery

Mohs micrographic surgery (MMS) is a microscopically controlled, tissue-sparing surgical technique that allows histological evaluation of the peripheral margin in the course of the surgical procedure [49]. The tumor is surgically removed layer by layer and each layer is examined microscopically on site, with the removal continuing until no abnormal cells remain. A randomized trial comparing standard surgical excision and MMS for the treatment of 408 primary and 204 recurrent facial BCCs reported 5- and 10-year recurrence rates of 2.5% and 4.4% for primary BCCs treated by MMS, and 4.1% and 12.2% for primary BCCs treated by standard excision, respectively. For recurrent BCCs, the 5-year recurrence rates were 2.4% for MMS and 12.1% for standard excision [50–52]. In the series of 560 primary periocular BCCs treated with MMS, the 5-year recurrence rate was 0% [53]. Thus, according to these studies, MMS is more efficacious than conventional surgical excision in the complete removal of BCCs. However, the procedure is time consuming and more expensive than conventional surgical excision [54]. Since other treatment methods achieve similar efficacies in low-recurrence risk BCCs, MMS is more appropriate for the treatment of high-recurrence risk tumors.

Electrodesiccation and curettage

In this procedure, the tumor surface is removed with a blade or scraping device, and the remaining base is seared with an electric needle to control bleeding and destroy residual tumor cells. An oozing crust remains that usually heals within 6 weeks. Although ED&C is fast and easily performed, histologic confirmation of tumor removal is impossible; hence, the tumor recurrence rate depends on

the experience of the surgeon. A review of six studies including 4212 BCC patients treated with ED&C reported recurrence rates ranging from 5.7 to 18.8% [55]. A single-institution study analyzing the efficacy of ED&C for 2314 BCCs reported recurrence rates of 3.3% for lesions involving low-risk areas regardless of tumor size, 4.5% for lesions < 6 mm in high-risk areas, and 17.6% for lesions > 6 mm in high-risk areas [56]. Therefore, ED&C is more suitable for BCCs without aggressive histopathological features and located in low-risk areas [57].

Cryosurgery

The direct application of liquid nitrogen onto the tumor results in the formation of extra- and intracellular ice crystals, thus impairing the cellular phospholipid membrane and damaging the surrounding tumor-associated vessels [58]. Although cryosurgery is easily performed, tumor removal cannot be histologically confirmed. The reported efficacy of cryosurgery is variable and depends on the treatment procedure. A single-institution study analyzing the efficacy of deep cryosurgery for 4406 non-melanotic skin cancers determined a 98.6% cure rate [59]. Meanwhile, a review of six studies including 796 BCC patients treated with cryosurgery found the recurrence rates ranging from 3.5 to 16.5% [55]. A non-randomized study comparing cryosurgery and radiation therapy (RT) revealed the inferiority of cryosurgery, based on 2-year recurrence rates of 39% and 4%, respectively [60]. In a randomized trial comparing surgical excision and a combination of curettage and cryosurgery, the recurrence rate was 8.2% and 17.6%, respectively, indicating the inferiority of cryosurgery, even when combined with curettage, compared to surgical excision [61]. Furthermore, the cosmetic outcome of cryosurgery is also inferior to surgical resection [62]. For these reasons, cryosurgery should not be the first-line treatment of BCC, especially for tumors with a high recurrence risk or if treatment is likely to result in a poor cosmetic outcome.

Topical imiquimod

Imiquimod is an immune response modifier that induces monocytes, macrophages, and dendritic cells to produce the cytokines that stimulate cell-mediated immunity. It also promotes the apoptosis of tumor cells, by circumventing their anti-apoptotic mechanisms [63].

In two identical randomized trials for 724 superficial BCCs, 5% imiquimod cream or vehicle was applied once daily, five or seven times per week, for 6 weeks. Histological clearance rates 12 weeks post-treatment were 82% in the five-times imiquimod group, 79% in the seven-times imiquimod group, and 3% in the vehicle group. The severity of erythema, tumor thickness, erosion, and scabbing/crusting after treatment were associated with the efficacy of the drug [64]. A retrospective study of 127 superficial BCCs also reported an association between the efficacy of imiquimod and tumor thickness, based on recurrence rates of 0% (0/108 cases) in tumors ≤ 0.4 mm deep and 57.9% (11/19 cases) in those > 0.4 mm deep; the mean follow-up period was 34 months [65]. In addition, the efficacy for nodular BCCs is relatively low. Two randomized trials for 56 nodular BCCs treated with imiquimod once daily, 7 days per week for 6 and 12 weeks, reported a histological clearance rate of 76% and 71%, respectively [66]. The histological clearance rates in 90 nodular BCCs treated three

times with imiquimod for either 8 or 12 weeks was 63.7% [67]. However, the efficacy of imiquimod is inferior to that of surgical excision. An unblinded, parallel-group, non-inferiority trial comparing surgical excision of BCCs in low- or medium-risk areas with 4-mm surgical margins vs. the treatment of similar tumors with 5% imiquimod cream once daily for 6 weeks showed 98% and 85% cure rates for superficial BCCs, and 99% and 83% cure rates for nodular BCCs, respectively [68]. The local side effects of imiquimod are skin irritation and hypopigmentation within the treated area. Systemic side effects include fatigue, influenza-like illness, exfoliative dermatitis, and angioedema [68]. Based on these reports, imiquimod is usually indicated for the treatment of superficial BCCs in low-risk sites [68, 69•].

Topical fluorouracil

The pyrimidine analog fluorouracil (FU) is an antineoplastic antimetabolite that interferes with DNA synthesis by inhibiting thymidylate synthetase [70]. A 5% cream or solution of FU is topically applied for the treatment of BCC.

In a randomized trial comparing FU, imiquimod, and photodynamic therapy (PDT) for superficial BCCs, the histological clearance rate of 5% FU cream at 3 and 12 months was 80.1% and the 5-year tumor-free survival rate following twice-daily application for 4 weeks was 70%. The corresponding values for imiquimod, however, were 83.4% and 81%, indicating the inferiority of FU [71, 72•]. The efficacy of FU in the treatment of non-superficial, recurrent, and other high-risk BCCs is also low [73, 74]. Furthermore, topical treatment of these high-risk subtypes can lead to a false impression of cure, although the dermal lesion remains. The side effects of FU include scarring, determined in 9–16% of superficial BCCs and squamous cell carcinomas in situ [75]. In addition, areas near the eyes, lips, and nose are sensitive to the drug. For these reasons, topical FU is usually indicated only for superficial BCCs in noncritical anatomical areas, whereas it is generally contraindicated for nodular or aggressive BCCs [75].

Photodynamic therapy

During PDT, the lesions are usually exposed to a beam of visible light (400–450 nm or 630–635 nm) for several hours after the direct application of photosensitizing porphyrins such as 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) [76]. Reactive oxygen species generated by the selective absorption of light by the photosensitizer induces cytotoxicity for the tumor cells and a local inflammatory reaction that may contribute to tumor destruction [77]. While PDT is less invasive, the histologic confirmation of tumor removal is not possible. The cure rates are variable, with complete tumor removal depending on the concentration of photosensitizers within the tumor cells and the light-focusing ability of the involved area [78].

Superficial BCCs are more responsive to PDT than other subtypes, as demonstrated by their 72–100% cure rates [71, 78, 79]. In a randomized trial comparing MAL-PDT and surgical excision with 3-mm surgical margins for 196 small superficial BCCs, the 12-month post-operative recurrence rate was 9% and 0%, respectively [80]. Another randomized trial comparing FU, imiquimod, and MAL-PDT for superficial BCCs reported a 3- and 12-month histological clearance rate with MAL-PDT of 72.8% and a 5-year tumor-free

survival rate of 63%. The corresponding rates with imiquimod were 83.4% and 81%, suggesting the inferiority of MAL-PDT [71, 72•]. Nodular BCCs are less likely to respond to PDT because the light cannot penetrate far enough into the lesion [81]. In a randomized study comparing MAL-PDT with surgical excision for 105 nodular BCCs, the estimated 5-year post-treatment complete response (CR) rates were 76% and 96%, respectively [82]. Major side effects are prolonged photosensitivity and irritations at the treated site. Nevertheless, PDT resulted in a significantly better cosmetic outcome than achieved with surgical excision [82]. PDT is approved in many European countries for the treatment of BCC, mainly primary superficial BCCs at low-risk sites.

Radiation therapy

The advantage of RT is that it spares structures of cosmetic or functional importance. Reported overall 5-year cure rates are 91–93% for previously untreated BCCs and 86–91% for recurrent BCCs [83–86]. However, BCCs that recur following RT may behave more aggressively, including a second recurrence and distant metastasis [87]. In addition, although evidence regarding the long-term efficacy of RT is limited, delayed side effects within the treatment field, such as chronic radiation dermatitis, permanent alopecia, dermal and subcutaneous fibrosis, necrosis, and secondary cutaneous malignancies, have been reported [8]. Furthermore, the favorable cosmetic results may deteriorate with time [88]. RT is, therefore, generally reserved for patients ineligible for surgical therapy, particular those with tumors in high-risk areas.

Intralesional treatments

Although rarely used in the current management of BCCs, intralesional injection of interferon (IFN), FU, or bleomycin provides a treatment option for patients who are not eligible for surgical therapy. A systematic review determined cure rates of 68%, 76%, and 63% in patients treated with IFN-α2a, IFN-α2b, and IFN-β, respectively. Systemic side effects are fever, malaise, and headache [89]. While studies on the results achieved with FU and bleomycin injections are limited, one systematic review reported cure rates of 100% in 23 BCCs treated by FU injection and 100% for 11 BCCs treated with bleomycin injection [89].

Treatment of locally advanced and metastatic BCCs

The metastasis of BCCs usually occurs in association with deeply invasive lesions or those > 10 cm^2 in diameter [90]. The estimated rate of BCC metastasis ranges from 0.0029 to 0.55%, with regional lymph nodes, lungs, bones, skin, and liver as common metastatic sites [90, 91]. The prognosis of patients with metastatic BCC (mBCC) is poor. A literature review of 194 published cases reported a median survival time of 10.0 months (range: 0.5–108.0 months) after detection of the metastasis [91]. However, these data were mainly those of patients treated with conventional multidisciplinary therapies, whereas a determination of the prognosis of patients treated with emerging therapies, such as SMO inhibitors, awaits further investigation.

SMO inhibitors

Vismodegib and sonidegib are oral, small-molecule inhibitors of SMO that inhibit HH signaling activation [13, 92]. An open-label trial of vismodegib for 1119 locally advanced BCCs (laBCCs) determined a response rate (RR) of 68.5%, including a CR rate of 33.4% and a partial response (PR) rate of 35.1%. The RR in 96 mBCC patients was 36.9%, with CR and PR rates of 4.8% and 32.1%, respectively. Median progression-free survival was 23.2 months in laBCC and 13.1 months in mBCC [93]. In a randomized trial of two different doses of sonidegib for 66 laBCCs and 13 mBCCs, the group receiving 200 mg/day had a RR of 57.6% and 7.7%, respectively. The disease control rate, including stable disease, was 91.9% in laBCC and 92.3% in mBCC [94, 95]. However, tumors may develop resistance to SMO inhibitors. A single-institution analysis reported that 21% (6/28) of patients with laBCC or mBCC developed at least one regrowth while undergoing vismodgib treatment, with a median time to regrowth detection by clinical examination of 56.4 weeks [96]. Although further evidence is necessary to establish the efficacy and safety of SMO inhibitors, a meta-analysis of 18 studies in the literature found similar overall response rates (ORRs) for vismodegib and sonidegib in the treatment of laBCCs (68.8% vs. 56.6%), but very different CR rates (30.9% vs. 3.0%). In mBCCs, the ORR of vismodegib was 2.7-fold higher than that of sonidegib (39.7% vs. 14.7%). Side effects of either drug include muscle spasms, dysgeusia, and alopecia, with a combined prevalence of 67.1%, 54.1%, and 57.7%, respectively [97•].

Cytotoxic chemotherapy

Because of the rarity of mBCC, only a few small case series are available regarding the efficacy of conventional cytotoxic chemotherapies. In a review of 12 reported cases involving treatment with platinum-containing regimens, five CRs and four PRs were achieved [98].

Summary

Generally, BCCs have a low metastatic potential and follow an indolent clinical course. However, tumor infiltration may lead to recurrence. The risk of recurrence depends on several factors, including the tumor site and histopathological subtype. A pre-treatment clinicopathological assessment of the recurrence risk is therefore necessary to select the optimal treatment strategy. For the treatment of primary lesions, conventional surgical excision is the standard. However, other therapeutic options may also be appropriate, depending on the tumor site, pathological subtype, the patient's condition, cosmetic outcome, and the cost of treatment. The prognosis of patients with mBCC is unclear due to the rarity of these cases. However, emerging SMO inhibitors have thus far shown impressive results in tumor shrinkage, and their use is expected to prolong patient survival.

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Compliance With Ethical Standards

Conflict of Interest
Keiji Tanese declares that he has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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