Dermatology

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Basal cell carcinoma

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Basal cell carcinoma (BCC), an essentially indolent, locally invasive epidermal malignancy, is now the commonest tumour affecting white populations. Metastases are rare but BCCs destroy surrounding tissue and can cause considerable morbidity, particularly on the head and neck. Worldwide incidence is increasing by about 10% per annum, so the prevalence of BCC will soon equal that of all other cancers combined.[1] There is marked geographical variation in incidence: in the UK (Welsh data), the age-standardised annual incidence was estimated as 114.2 per 100,000 population in 1998,[2] while in Australia the figure is much higher at 726 per 100,000.[3] Of those developing a BCC, 50% will develop another within 5 years. The age-standardised incidence of BCC in white populations is 20–40% higher in men, BCC is uncommon in dark skinned races and sporadic cases are rare before age 20.

Pathogenesis and risk factors (Table 1)

Ultraviolet (UV) radiation is regarded as critical in the pathogenesis of BCC but the precise relationship remains obscure. Many BCCs arise on the trunk, an area traditionally having limited exposure. Frequent sun exposure during childhood and episodic sunburn seems to increase risk, as does tendency to freckle. However, occupational exposure to the sun and sunburn as an adult (>20 years) does not seem to factor. Fitzpatrick skin type I (always burns, never tans), red or blond hair and blue or green eyes have been shown to be associated with increased risk of BCC development. Positive family history, ionising radiation, low vitamin intake, high dietary energy, especially from fats, various chemical (particularly arsenic from 'tonics') and dust exposures predispose to BCC development.[4] Immunosuppressive therapy also increases risk (tenfold in renal transplant recipients[5]). Psoralen and UVA (PUVA) treatment, classically for psoriasis, carries a modest increased risk.

Several genodermatoses are associated with the development of BCC, including albinism, xeroderma pigmentosa, Bazex's syndrome and the naevoid BCC syndrome (Gorlin's syndrome), an autosomal dominant disorder in which multiple BCCs develop with associated palmer and plantar pits, jaw cysts, spine and rib abnormalities, calcification of the falx cerebri and cataracts.

Phenotypes

The likelihood of development of BCC seems to depend on a complex interplay between intensity and length of exposure to UV irradiation, but this does not explain the large variation in presentation. Studies of these phenotypic differences have so far demonstrated two groups:

- *Clusters of BCC* [multiple presentation type, (MPP)]: patients have 2–5 BCCs at presentation and a

Key Points

Basal cell carcinoma (BCC), an essentially indolent, locally destructive epidermal malignancy, is the commonest tumour affecting white populations

The overall worldwide incidence of BCC is increasing by approximately 10% per annum, so its prevalence will soon equal that of all other cancers combined

Ultraviolet radiation is regarded as critical in the pathogenesis of BCC but the relationship remains obscure

Immunosuppressive therapy in renal transplant recipients increases tenfold the risk of developing BCC

There are several clinical and histological variants of BCC of which the morphoeic variant is the most aggressive

KEY WORDS: basal cell carcinoma, genodermatoses, Gorlin's syndrome, Mohs' micrographic surgery, non-melanoma skin cancer, photodynamic therapy

Table 1. Risk factors for basal cell carcinoma.

- Increasing age
- Male sex
- Fitzpatrick skin type I
- Red or blond hair
- Blue or green eyes
- Freckling in childhood
- Sunburn in childhood
- Positive family history
- Certain genodermatoses
- Immunosuppression
- Exposure to ionising radiation
- Exposure to arsenic
- PUVA treatment

PUVA = psoralen and ultraviolet A.

proportion subsequently have several clustering events, a feature which appears to have a strong genetic predisposition.[6,7]

- *Truncal tumours*: evidence suggests that different mechanisms mediate the development of BCC on the trunk. Individuals with truncal tumours develop more BCCs, are younger at onset and develop more BCC clusters than those not having truncal tumours. In addition, first presentation with a truncal tumour is associated with the development of significantly more subsequent BCCs at this site than in those presenting with head and neck lesions.

These two identified phenotypes show associated gene polymorphisms in both the glutathione S-transferase (GST) and cytochrome P450s (CYP) families. CYP2D6 and GSTT1 are associated with BCC susceptibility, whereas CYP2D6, together with vitamin D receptor and tumour necrosis factor alpha are associated with increased numbers of BCCs.[8]

Lesions

Approximately 80% of BCCs arise on the head and neck, the rest on the trunk and lower limbs. Early lesions are usually translucent with a raised edge and scattered telangiectasia. Several clinical and histological variants are described: the classical 'rodent ulcer' (Fig 1) with an ulcerated centre; nodular (Fig 2) or cystic; morphoeic (Fig 3); superficial spreading (Fig 4); and pigmented. Of these, the morphoeic variant is the most aggressive, with ill-defined borders making direct excision difficult. They can look quite atypical, can present late and may need specialised surgery for maximal conservation of unaffected tissue.

Metastatic disease

Metastatic BCC is a relatively rare event (reported incidence 0.03%). It tends to occur on a background of large (>20 cm) neglected tumours on the head and neck, mainly in men. There is less than 20% survival at 1 year and approximately 10% survival at 5 years. Occasionally surgical resection of metastatic disease is possible; cases should be referred to specialist centres for full assessment.[9]

Other malignancies

The risk of developing a squamous cell carcinoma is increased slightly after developing a BCC (6% risk at 3 years)

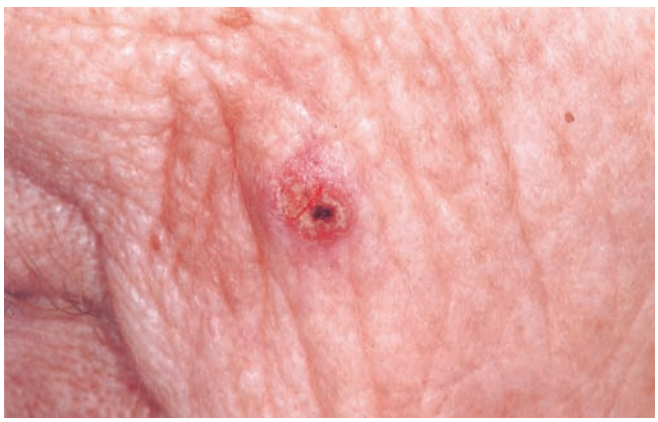

Fig 1. Classical 'rodent' ulcer on the cheek.

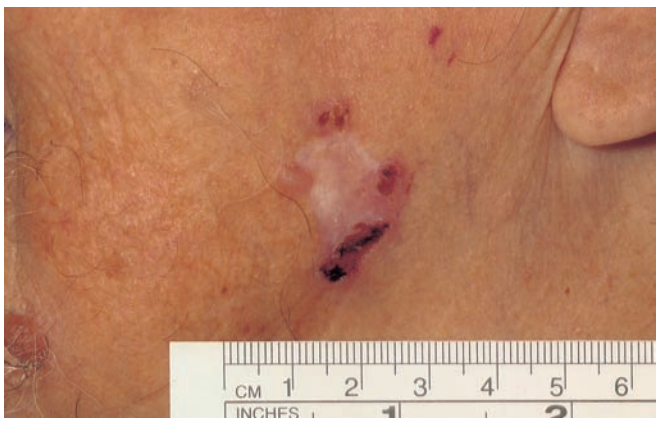

Fig 3. Morphoeic basal cell carcinoma on the cheek.

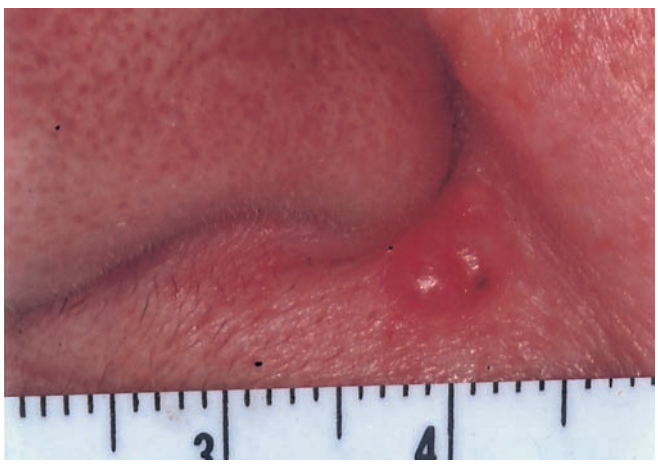

Fig 2. Nodular basal cell carcinoma just beneath the left alar of the nose.

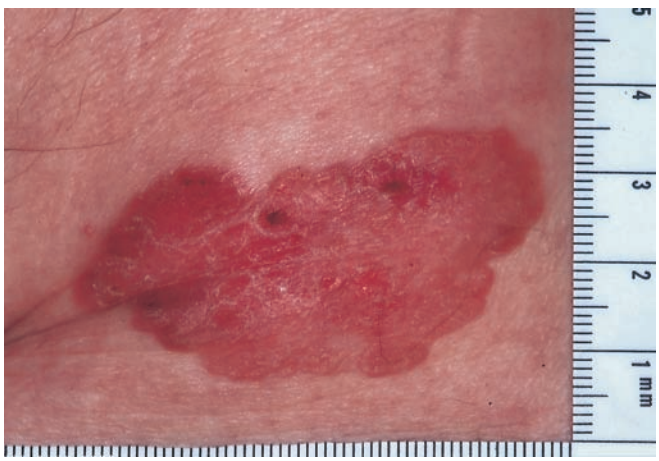

Fig 4. Large (5.5 cm x 3.5 cm) superficial spreading basal cell carcinoma on the lower abdominal wall.

Figs 1–4. Copyright: Medical Illustration, Hope Hospital, Salford Royal Hospitals.

and there is also a higher risk of developing a malignant melanoma. An American study showed a multivariate risk of 2.2, presumably related to UV radiation exposure.[4]

The relationship of development of other malignancy after development of a BCC is uncertain – some studies have shown a small increased risk with cancer of the lung, thyroid, mouth, breast and cervix and non-Hodgkin's lymphoma, whilst others have shown no association. Recent work supports the evidence for an association by the finding of increased cancer mortality in patients with BCC (relative risk 1.23, 95% confidence interval 1.15–1.32 for men). Further work is needed to increase understanding of these associations.[4]

Treatment

Several different modalities are used in the treatment of BCC[10] (Table 2). Careful selection is essential and depends upon individual factors. A biopsy of the lesion prior to definitive treatment can help guide choice. Essentially, the method chosen should take into account the prognostic factors for the tumour under consideration (Table 3), local facilities available, operator expertise and any comorbidity.

Surgery

An advantage of surgical treatments is the histological examination of tumour margins to establish clearance. Mohs' micrographic surgery (MMS) is a specialised technique that uses horizontal frozen sectioning to examine serial sections of tissue until all margins are free of tumour. A study using MMS for excising primary (ie previously untreated BCC) found that for small (<20 mm) well defined tumours 3 mm surgical margins gave tumour clearance rates of 85%, whereas 4–5 mm margins gave clearance rates of 95%.[11,12] Large and morphoeic BCCs require wider margins to achieve complete histological resection (13–15 mm surgical margins for 95% clearance).[11]

MMS gives high cure rates for tumours in high-risk sites with maximal conservation of uninvolved tissue. The suggested overall 5-year cure rates for primary and recurrent BCC are 99% and 94.4%, respectively.[13,14]

Other destructive techniques

Curettage and cautery (scraping away the lesion and cauterising bleeding points) and cryosurgery (liquid nitrogen at –196° C) are two other destructive techniques for the treatment of BCC. Operator skill and appropriate choice of lesion are necessary to ensure the best clearance rates (ca 95%).[10,15] Problematic wounds, with subsequent poor cosmesis, are occasional sequelae.

Photodynamic therapy

Photodynamic therapy (PDT), which uses the intrinsic cellular haem biosynthetic pathway and photo illumination to initiate tumour cell destruction, is a relatively new treatment for superficial BCCs, which is increasingly available for superficial non-melanoma skin cancers. After topical application, precursor molecules are selectively concentrated in tumour tissue where they undergo further metabolism. After irradiation by visible light of a certain wavelength, these molecules become excited and jump to a higher energy level. Upon release of this energy, reactive oxygen species are released; these cause cellular destruction, and so resolution of the tumour – without scarring. (It is thought that, fundamentally, holes are punched into cellular organelles, especially mitochondria, so the cells can no longer function.)

This procedure causes cell death in two ways: through cellular damage and apoptosis. The best clearance rate (96% at 12 months) is achieved with two exposures 1 week apart. PDT offers patients with large and/or multiple superficial BCCs particular benefits as it gives a low rate of adverse events with good cosmetic results by selectively targeting tumour cells.

Radiotherapy

Radiotherapy is an effective treatment for many BCCs, with high cure rates up to 91% at 5 years. It is not recommended for large tumours in critical sites, areas subject to repeated trauma such as the extremities and for young patients, as late changes in irradiated skin can result in poor cosmesis. It cannot be repeated

Table 2. Treatment options for basal cell carcinoma.

Surgical	Excision Mohs' micrographic surgery
Destructive	Cryosurgery Curettage and cautery
Non-surgical	Photodynamic therapy Radiotherapy Topical: • 5-fluorouracil • imiquimod

Table 3. Recognised prognostic factors for basal cell carcinoma (BCC). Increased risk of recurrence is more likely if features listed below are present.

Tumour site	Central face (eyes, nose, naso-labial folds, lips) and ears
Tumour size	Recurrence rates rise significantly with increasing tumour size
Tumour type and definition of margins	For a small (<20 mm), well defined BCC, peripheral tumour excision margins of 3 mm achieve clearance in 85% of cases; a 4–5 mm excision margin is required for clearance rates of the order of 95%
Growth pattern/Histological type	Morphoeic, micronodular and infiltrative BCCs are more likely to recur
Treatment failure/Recurrence	Previous treatment failure and/or recurrence can result in problematic tumours that are difficult to treat: eg radiotherapy cannot be repeated and can lead to atrophic skin changes that delay subsequent healing if surgery is then attempted
Immunocompromised patients	Immunosuppression can lead to the development of aggressive tumours

in the same area and subsequent management of recurrent tumours can be difficult.

Topical preparations

Topical 5-fluorouracil cream is useful for low-risk tumours on the trunk and limbs, but there is a high incidence of local side effects. A new topical formulation (5% imiquimod cream) has recently been licensed for superficial BCCs; it has shown promise so far, but there is little long-term follow-up data. It appears to be relatively well tolerated, the incidence of side effects being related to the frequency of application.

Recurrent tumours

Particular management difficulties are posed by recurrent tumours. In general, they are best treated by Mohs' micrographic surgery in high-risk sites and excision elsewhere.

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