Eruptive Disseminated Superficial Basal Cell Carcinomas 24 Years after Bone Marrow Transplantation

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Introduction

Patients treated with allogeneic bone marrow transplantation (BMT) are susceptible to the development of various secondary tumours, either internal or involving skin and/or mucosae [1]. These tumours usually occur within the first 15 years following the BMT procedure. Several risk factors for the development of such malignancies have been identified including the use of total body irradiation as part of the conditioning regimen, prior radiotherapy, but also immune parameters such as HLA-mismatched allograft, graft versus host disease (GvHD), immunosuppressive regimen and age at transplantation [2]. Within the spectrum of skin carcinomas occurring in transplant recipients, basal cell carcinomas (BCC) appear clearly as the most frequent ones [3]. However, series of marrow graft recipients did not give precise details about the possible occurrence of a high number of lesions in a specific individual [3–6]. We report here the case of a 67-year-old male patient who developed 24 years after BMT more than 40 superficial BCC as well as a few nodular BCC. These tumours were mainly found on the lower limbs at sites without sun exposure. The patient was treated with surgical excision of nodular BCC while photodynamic therapy was used for the superficial BCC. No recurrences were reported at 5-year follow-up. To our knowledge, this is the first case of a patient presenting eruptive and non-recurring BCC so long after BMT. Only two similar cases have been reported in other circumstances. There is no clear explanation to this peculiar non-recurrence. We speculate that repair of DNA mutations may have occurred.

Case Presentation

A 67-year-old male was referred in 2008 for multiple erythematous cutaneous lesions. The patient indicated that the lesions developed quickly in the previous months before seeking medical advice. He had been treated with allogeneic BMT in 1984 for chronic myelogenous leukaemia. The conditioning regimen consisted of a 10-Gy total body irradiation and intravenous cyclophosphamide at the dose of 120 mg/kg. He received systemic prevention of GvHD with methotrexate, at a time when a single agent was used as GvHD prophylaxis. During his follow-up, the patient presented features of limited chronic GvHD 6 months following BMT and he was treated with steroids for 1 year with complete remission. Upon his first visit in the dermatology department, he was receiving only nicardipine and glimepiride for hypertension and diabetes. Physical examination disclosed more than 40 lesions on the legs, thighs, back, and wrists (fig. 1). These consisted in erythematous macules 5–10 mm in diameter. Biopsies of 5 different lesions demonstrated in all of these the same typical aspect of superficial BCC. There were also several different lesions on the right ear, back and left ankle. The biopsies indicated the presence of nodular BCC at all these sites. The patient’s phototype was 3 and he...
had been well educated to avoid sun exposure. Two sessions of photodynamic therapy were performed on the erythematous macules and allowed a complete disappearance of the superficial BCC lesions. The nodular BCC were surgically removed. Five years later, the patient did not show any recurrence.

Discussion

This case is featured by the rapid development of disseminated superficial BCC late after BMT. A large body of literature has already shown that such transplant patients have increased risks of developing various solid cancers. Indeed, the cumulative incidence rates were 2.2 and 6.7% at 10 and 15 years after BMT, respectively. This corresponds to a relative risk of 8.3 times more cancers as compared to the general population 10 years after transplantation [1]. The spectrum of secondary extracutaneous solid malignancies concerns mainly melanoma, cancers of the oral cavity, brain, liver, thyroid, bone and connective tissues [1]. Risk factors for such tumours varied depending on studies. Curtis et al. [1] have demonstrated that an older age at transplantation as well as higher doses of total body irradiation were associated with an increased risk of secondary tumours. However, concerning skin malignancies, other authors have indicated that young age and/or immune parameters such as chronic GvHD and use of immunosuppressive regimens were associated with increased risk [3]. Some studies suggest that GvHD and its therapy may increase the risk for solid cancers, particularly squamous cell carcinomas (SCC) of the buccal cavity and skin [7]. Of note, SCC of the skin appeared to be more frequent in males and related to the duration of chronic GvHD [7]. A large study has focused on skin secondary malignancies [3]. The 20-year cumulative incidences of BCC and SCC were 8.4 and 5.5%, respectively. Multivariate analysis indicated that young age at the time of BMT, total body irradiation in the conditioning regimen, white race and chronic GvHD were significant factors for BCC [3]. However, the authors insisted on the bias that may result from underreporting cases of BCC.

Post-BMT BCC are usually characterized by one, or more rarely, few lesions, the maximum being 3 in 1 patient [3–6]. Our patient, in contrast, was a peculiar case characterized by more than 40 superficial BCC. Such features can be found in Gorlin’s syndrome (basal cell naevus syndrome) as well as in arsenic intoxication [8]. However, besides such genetic or chemical-induced diseases, only 2 cases similar to our patient have previously been reported. One concerned a 55-year-old male presenting with 43 superficial BCC 20 years after treatment of an immunoblastoma with cobalt irradiation [8]. The other case recently reported described a 55-year-old man with 27 superficial BCC developing over the course of approximately 12 months in the setting of human immunodeficiency virus infection [9]. Intriguingly, this last patient noted a rapid increase in lesion development when he began antiretroviral therapy, which may suggest a relationship between immune reconstitution and the genesis of neoplasms. No genetic studies were undertaken. Therefore, it appears that multiple and eruptive superficial BCC is a possible although very rare event triggered by radiation and/or immunosuppression.

The study of the autosomal dominant Gorlin’s syndrome – characterized by the development of multiple BCC – has revealed the implication of the Sonic hedgehog (Shh)-pathway mutations in this syndrome. Later on, the role of the same molecular mutations was demonstrated in sporadic BCC. Therefore, in contrast to most cancers, where several mutations occur, BCC appear to critically depend on abnormalities of a unique signalling pathway, the Shh pathway. These abnormalities consist either in inactivating mutations in the Shh receptor Patched (PTCH) or...
inactivating mutations in its co-receptor Smoothened (Smo). Current evidence suggests that Shh pathway deregulation alone can rapidly generate BCC directly from normal keratinocytes. This may explain why, in contrast to melanoma and SCC, BCC has no apparent precursor lesion. Interestingly, superficial BCC were also recently shown to result from a monoclonal proliferation of Shh-mutated cells [10].

The patient described here has several original characteristics. He is to our knowledge the first presenting with dozens of BCC after BMT or any transplant procedure. Moreover, he developed all these lesions as a unique acute episode of ‘eruptive’ superficial BCC 24 years after the conditioning regimen without any previous occurrence. The lesions predominated on the lower limbs, a site with no other signs of helioderma. As mentioned above, total body irradiation is considered as the most important triggering phenomenon in cutaneous secondary tumour development especially in young recipients, and additional events – such as sun exposure – can interfere, which was not the case in our patient. There is no recurrence after a 5-year follow-up, which is also an unexpected event. Analysis of the incidence of skin carcinomas developing after BMT indicates that the curve continues usually to increase even 20 years after grafting [3]. The mechanism of an acute isolated and transient cutaneous carcinogenesis remains unexplained. As mentioned above, there is strong evidence that Shh pathway deregulation is a key event in BCC pathogenesis including superficial BCC. However, this has not been checked in cases such as post-transplantation BCC, neither in ours. One could speculate that DNA mutations were present only at the skin cancer sites due to an additional external event arising there. However, the non-recurrence as well as the dissemination makes this possibility unrealistic. Our speculative hypothesis would be therefore that the non-recurrence of any tumour would indicate that DNA mutations were present only at the skin cancer sites due to an additional external event arising there. In conclusion, eruptive disseminated superficial BCC remain a very rare event that may be triggered late after BMT as in our case but also after cobalt treatment or arsenic exposure. Such a rare phenomenon remains unexplained but raises both the questions of its delayed occurrence as well as its unexpected non-recurrence.

**Author Contributions**

Dr. Almidimeegh analysed the case and wrote the draft, Dr. Mougeuet analysed the slides, Dr. Guegan and Dr. Aractingi saw the patient, analysed the case and reviewed the manuscript. All above authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, study concept and design.

**Disclosure Statement**

No financial disclosure reported concerning this article.

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**References**


