CORRESPONDENCE

Long-term skin findings in patients with Fanconi anemia after allogeneic hematopoietic stem cell transplantation

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TO THE EDITOR:

Hematopoietic stem cell transplantation (HSCT) is the only therapeutic option that can restore normal hematopoiesis in patients with Fanconi anemia (FA) [1]; however, FA patients that undergo HSCT are at risk for long-term complications due to transplant-related factors or due to secondary FA-related issues unrelated to transplantation, including complications of congenital anomalies, endocrinopathies, and an increase in cancer susceptibility [2, 3]. As such, recent guidelines recommend post-HSCT skin cancer screening in FA patients every 6–12 months [4].

This single-center, cross-sectional study aimed to present the outcomes and long-term skin findings of 18 FA patients that underwent allogeneic HSCT at Hacettepe University, Ankara, Turkey, between 2006 and December 2016, so as to make recommendations for dermatologists following-up such patients. Patients were followed-up by a multidisciplinary team at the Pediatric Bone Marrow Transplantation Unit, including experienced specialists of dermatology, ophthalmology, otolaryngology, urology, endocrinology, nephrology, gastroenterology, and cardiology. The study protocol was approved by the Institutional Ethical Committee, and all patients or their legal guardians provided written informed consent.

Demographic characteristics, age at the time of HSCT, dermatological examination findings, history of acute, and/or chronic graft-versus-host disease (GvHD), comorbidities, malformations, and anomalies of either the endocrine, renal, or cardiac systems were recorded. All patients underwent careful dermatological examination by two dermatologists and, if present all oral, genital, scalp, and nail lesion were noted. In cases of a suspicious lesion, following photo documentation and digital dermoscopy the lesion was biopsied or followed-up every 3–6 months, according to the provisional diagnosis.

HSCT was indicated in all the patients due to bone marrow failure. A fludarabine-based conditioning regimen was used in all patients. Cyclosporin A and low-dose methotrexate were administered for GvHD prophylaxis. In all, 12 of the patients received bone marrow grafts and 6 received peripheral blood stem cell products from HLA-matched related donors. Grade 1 acute GvHD with skin involvement only developed in one patient and resolved completely following short-term corticosteroid treatment in addition to cyclosporine. None of the patients had chronic GvHD. Complete donor chimerism (>95%) was achieved in all the patients and graft failure was not observed beyond 2 years following HSCT.

Mean age of the patients (11 males and 7 females) at the time of HSCT and at the last post-HSCT dermatological examination was 8.6 ± 4.7 years and 18.2 ± 5.2 years, respectively. The patients were followed-up by the dermatology department for a median 7 years post-HSCT (range: 2–24 years). Among the patients, three had a thumb deformity (Fig. 1A), two had a radial ray malformation (radius agenesis ($n = 1$) and short radius ($n = 1$)), two had polydactyly, one had clinodactyly, one had pseudosyndactyly, one had hypoplastic auricula, one had cauliflower ears (Fig. 1B), and three had short stature and growth retardation. In addition, three patients had a congenital renal anomaly (ectopic kidney ($n = 1$), left kidney agenesis (n = 1), and pelvic kidney (n = 1)), two had urogenital abnormalities (bladder of diverticulum ($n = 1$) and hypospadias ($n = 1$)), and two had congenital heart anomalies (atrial septal defect ($n = 1$), and bicuspid aortic valve and patent foramen ovale ($n = 1$)), and one had facial paralysis and bilateral conductive hearing loss.

At the last post-HSCT follow-up dermatologic skin findings were café au lait macules ($n = 12$) (Fig. 1A, C), hypopigmented macules ($n = 7$, Fig. 1D), freckling ($n = 4$ (on the trunk: $n = 2$; on the face: $n = 1$; on the face, trunk, and upper extremities: $n = 1$)), diffuse hyperpigmentation ($n = 3$), atrophic stria ($n = 3$), keratosis pilaris ($n = 3$), eczematous plaques ($n = 2$), dyschromatosis ($n = 2$) (Fig. 1D, E), white plaques on oral mucosae ($n = 2$), nevus anemicus ($n = 1$, Fig. 1A), superficial basal cell carcinoma ($n = 1$, Fig. 1F, G), squamous epithelial hyperplasia ($n = 1$), and actinic keratosis ($n = 1$). Only one patient, a 29-year-old male, had concomitant superficial basal cell carcinoma and multiple actinic keratosis. This patient had a 6-month history of a round, erythematous, slightly raised, well-demarcated 2 × 2 cm plaque on the presternal skin (Fig. 1F–I) and numerous hyperkeratotic papules on his face (Fig. 1F, I). A 4-mm punch biopsy from the presternal skin was consistent with superficial basal cell carcinoma and imiquimod cream was prescribed. As the presternal lesion enlarged and the patient had severe itching and intense crusting after 4 weeks of imiquimod therapy, the treatment was discontinued and the lesion was totally excised; however, the excision specimen did not contain any residual tumor. The patient underwent one session of cryotherapy every 3 weeks for 2 months and all the papules completely resolved.

A 21-year-old male patient had painless, white plaques on his oral mucosa. Dermatological examination showed bilateral, well-demarcated, circumscribed, vegetative, non-ulcerated, thick, white, velvety, and minimally raised plaques on the buccal mucosae. Potassium hydroxide examination was negative for candida pseudohyphae. An incisional biopsy was performed due to the provisional diagnosis of leukoplakia and squamous cell carcinoma (SCC), and showed squamous epithelial hyperplasia without any neoplastic epithelial changes of the epithelium. Additionally, none of the patients had any suspicious lesions suggesting SCC and/or malignant melanoma on the skin, oral mucosa, genitalia, or nails.

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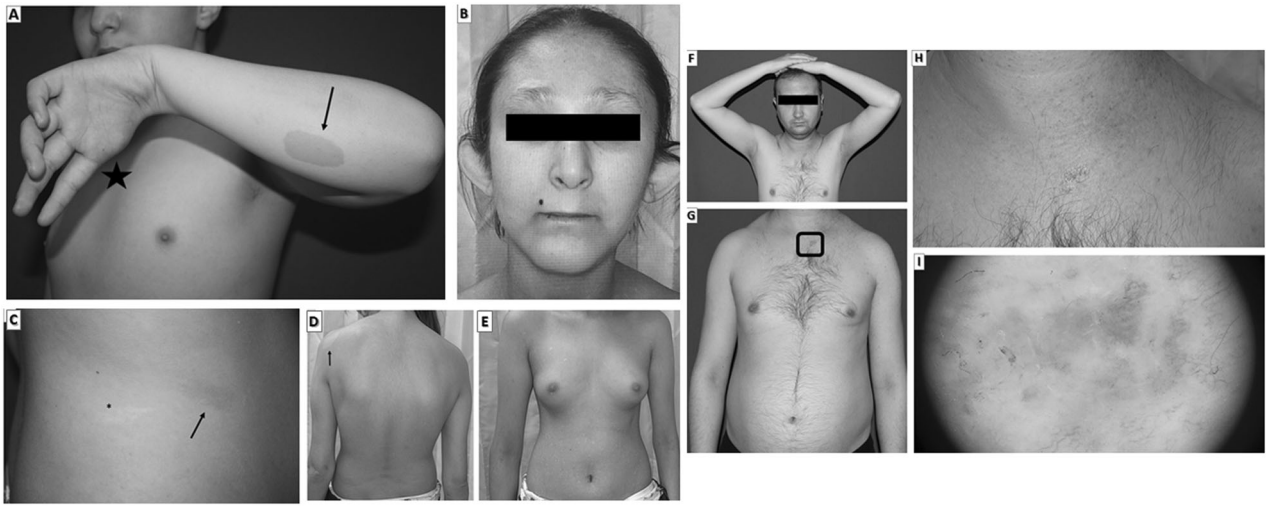

Fig. 1 The photographs of the patients and details are given below. A A 12-year-old male with a café au lait macule on the arm (arrow) and thumb agenesis (star). **B** A 17-year-old female with prominent and cauliflower ears. **C** A café au lait macule (arrow) and a nevus anemicus (asterisk). **D**, **E** A hypopigmented macule on the posterior of the left shoulder (arrow) and extensive dyschromatosis on the anterior and posterior aspects of the trunk. **F**, **G** A 29-year-old male with patchy freckling on the face, left side of the neck, right arm, and left axillary region extending to left shoulder. **H** An oval, erythematous, slightly raised, well-demarcated 2 × 2-cm plaque measuring on the presternal skin. **I** Upon closer dermoscopic inspection, the oval, reddish lesion contained dense thin telangiectasias and erosions.

Due to a defective DNA repair mechanism, FA patients have increased susceptibility to cancer, including leukemia, myelodysplastic syndrome, and SCC. In fact, they have a 500-fold higher risk of SCC, as compared to the general population [5]. Moreover, FA patients that undergo HSCT have a 4.4-fold higher risk of developing SCC of the anogenital, and head and neck areas than FA patients that do not undergo HSCT [6]. Kutler et al. [7] reported that the median age of onset of SCC in 754 FA patients was 31 years. Bonfim et al. [8] suggested that although HSCT can cure hematological complications allowing for survival to an age much older than normally expected for FA patients, there is a need to develop follow-up regimens, especially for early detection and management of SCC, which is fatal in its advanced stage; therefore, recent guidelines recommend skin cancer screening every 6–12 months for FA patients that have undergone HSCT [4].

Although these guidelines refer to the risk of skin cancer with regards to SCC in transplanted FA patients, it is equally important to follow-up these patients for malignant melanoma, as any patient that has undergone HSCT has an increased risk of new solid cancers, including malignant melanoma [9]. A cross-sectional study reported that among 93 FA patients, 6 patients had a history of basal cell carcinoma, with a mean age of onset of 25 years, 5 had a history of cutaneous SCC, with a mean age of onset of 27 years, and 2 had a history of melanoma diagnosed at age 38 and 42 years [10]. In the present study no cases of cutaneous SCC were observed, although one patient had both multiple actinic keratosis and superficial basal cell carcinoma at age 29 years.

It is important to note that immunosuppressed patients have a significantly higher risk of developing cutaneous malignancies, as compared to the general population [11]. As all the present study's patients received cyclosporin A and low-dose methotrexate for GvHD prophylaxis, cancer susceptibility other than defective DNA repair may be expected.

In conclusion, post HSCT follow-up regimens for FA patients should be improved and include a multidisciplinary team, which is crucial for early detection and management of cancers. Dermatologists can play a key role in the detection, prevention, and timely treatment of skin cancers in FA patients that undergo HSCT via regular follow-up.

ACCESS TO DATA AND DATA ANALYSIS

NA (corresponding author) had full access to all the study data and takes full responsibility for the integrity of the data and the accuracy of its analysis.

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AUTHOR CONTRIBUTIONS

NA, SE-E, and FVO contributed to the study's conception and design, and critically revised the manuscript. NA, SE-E, FVO, DUC, and BK contributed to collection of patient data and reviewed the manuscript. NA acquired the data, conducted the statistical analysis, and drafted the manuscript; she is the study guarantor.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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