Epidermolysis bullosa simplex (EBS) is a heritable skin disorder characterized by skin fragility and blistering. While its most severe variant, dystrophic epidermolysis bullosa (DEB) is associated with squamous cell carcinoma (SCC), the development of extracutaneous neoplasms in EBS is extremely rare. We report a novel case of supratentorial primitive neuroectodermal tumor (sPNET) in a 7-year-old male with EBS. Experience of radiation therapy and its challenges in children with EBS has rarely been reported. Pediatr Blood Cancer 2010;54:170–172. © 2009 Wiley-Liss, Inc.

INTRODUCTION

Epidermolysis bullosa (EB) is a heritable skin disorder characterized by increased skin fragility and blister formation after minor mechanical trauma. Three major inherited forms are EBS, junctional epidermolysis bullosa (JEB), and dystrophic epidermolysis bullosa (DEB) [1]. Phenotypic variants range from mild blistering largely localized to the hands and feet, to a more severe generalized form, leading to death in early infancy. EBS is the most common and the mildest form of EB and has three subtypes. They are EBS-Koeber, EBS Weber-Cockayne and EBS Dowling-Meara. Blistering in EBS usually occur in the intraepidermal area. EBS-Koeber commonly presents at birth to early infancy and involves the hands, feet and extremities. EBS Weber-Cockayne commonly occurs in children and adults and presents on the palms and soles only after a distinct traumatic event. EBS Dowling-Meara, a severe form of EBS, occurs at or shortly after birth with a generalized distribution of blisters [2]. Skin lesions in EBS usually heal without scarring and extracutaneous involvement is extremely rare. Evaluation of malignancies in EB shows that squamous cell carcinoma (SCC) is the most serious complication of EB in adults, especially those with DEB. By mid-adulthood, nearly all patients with DEB will have had at least one SCC and nearly 80% will have died of metastatic SCC despite aggressive surgical resection [3]. Central nervous system (CNS) tumors in children with EB are extremely rare. Only one case has been reported of an infant with JEB diagnosed with congenital rhabdoid tumor of the CNS at autopsy [4].

Supratentorial primitive neuroectodermal tumor (sPNET) in children are rare and represent less than 2.5% of childhood brain tumors, with the median age at presentation of 3 years. While the treatment for sPNETs is not well defined, current treatment involves a multifaceted approach that includes surgery, chemotherapy, and post-operative radiotherapy. However, sPNETs are more resistant to conventional treatment modalities, making them less curable than medulloblastomas. High-dose cyclophosphamide-based chemotherapy with stem cell support after risk-adapted craniospinal irradiation (CSI) results in excellent event free survival (EFS) in patients with newly diagnosed average risk (AR) sPNET [5]. Long-term neurocognitive toxicity and development of secondary malignancies are well-known complications of CSI. The tolerability of CSI in patients with EB and the long-term complications is unknown and has not been reported. However there are reports of radiation delivered locally to treat SCC in patients with underlying DEB [6]. This novel case demonstrates the presentation of a patient with EBS and sPNET and highlights the feasibility and successful use of CSI and focal tumor bed radiation.

CASE REPORT

A 7-year-old male presented with generalized hyperpigmentation of the skin at birth. A diagnosis of EBS was confirmed by skin biopsy. His skin blistered after minor trauma, which was managed symptomatically using emollients and topical antibiotics. One year prior to presentation, he started developing nonfocal headaches. Though initially mild, they increased over the following year and were associated with vomiting. These episodes were treated symptomatically as sinus infections. One week prior to admission, he developed ataxia and diplopia, with increasing intensity of headaches. He was evaluated in the emergency department, where a CT scan followed by an MRI showed a mixed cystic solid lesion in the left anterior temporal lobe. Following admission, he underwent a craniotomy and gross total resection of the left temporal lobe mass (Fig. 1). His spine MRI and CSF cytology were negative for any evidence of metastasis. Pathology was consistent with sPNET. Post-operatively his symptoms improved dramatically. Following GCSF stimulation, he underwent successful stem cell harvest. He was then treated with conventional CSI to a total dose of 23.4 Gy in 13 fractions. CSI was followed by a focal boost to the tumor bed using intensity modulated radiotherapy (IMRT) to a dose of 32.4 Gy in 18 fractions. Several important precautionary measures were taken to protect the patient’s underlying fragile skin condition from the effects of radiotherapy. Radiation therapy was administered in the supine position in contrast to the conventional prone position.

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The authors declare that there is no disclosure and any conflict of interest.

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Received 27 July 2009; Accepted 12 August 2009
The treatment couch as well as the customized head immobilization cushion was lined with cotton padding. The HeadFix device was fabricated with a nasal bridge rather than a conventional bite block. Petroleum jelly was liberally applied to the upper lip, nose, and other high friction points along with topical emollients to minimize the effects of friction injury. His skin toxicity profile was restricted to grades 1–2 (Fig. 2). This included small patches of moist desquamation in his ear folds and a few subcentimeter bullae on his occiput. Mild increase in his hyperpigmentation was seen during his radiation, which is slowly resolving. He had minimal nausea and vomiting, which were treated symptomatically and mild myelo-suppression during his radiation therapy. He is currently doing well and will begin four cycles of dose-intensive cyclophosphamide based chemotherapy with stem cell rescue.

**DISCUSSION**

The association of EB with brain tumors and its treatment has not been reported earlier. The only prior case report is of a male child with JEB who was found to have a cerebellar atypical teratoid rhabdoid (AT/RT) tumor at autopsy [4]. Due to the extreme rarity of this case, the tolerability of CSI is unknown in these patients. There are a few case reports of SCC in adult DEB patients, who were treated with localized radiation, but the toxicity was not reported...
would include increased incidence of SCC in these children. It remains to be seen how children with the EB and its variants would tolerate extended field radiation and whether long-term toxicities would include increased incidence of SCC in these children.

Radiation therapy is an important component of the multimodality treatment for children with sPNET. Though similar histologically to the medulloblastoma, the more distinct oncogenic pathways in these tumors make them different from their infratentorial counterparts [10]. They are very aggressive and have been treated with intensive therapy including CSI of 36 Gy. Several studies have supported the beneficial role of high-dose radiation treatment of the entire neuraxis as a critical part of the multimodality treatment for sPNET [11,12]. Though efforts have been devoted in various studies to eliminate, delay, or reduce dose and fields of radiation therapy, the results have met with reduced survival rates [13–15]. Thus, 36 Gy CSI remains an integral part of the multimodality therapeutic approach for children with these tumors. However, a recent study using reduced dose CSI of 23.4 Gy in AR patients followed by four cycles of high dose cyclophosphamide based chemotherapy with stem cell rescue showed a 5-year overall survival rate of 88 ± 13% survival [5]. Based on these promising data, we treated our AR patients with a reduced dose CSI of 23.4 Gy. This dose was hoped to reduce the long-term neurocognitive sequelae and development of secondary malignancies.

This report highlights several precautionary measures to potentially protect the integrity of the fragile skin in pediatric patients with EBS during radiation treatment. In addition, the case emphasizes the importance of the genetic and pathophysiologic associations between the development of brain tumors in children with underlying EB. Children with EB and brain tumors require a multimodality therapeutic approach to further define optimal treatment strategies.

REFERENCES