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CASE REPORT

Diffuse lung metastases in a child with blastic plasmacytoid dendritic cell neoplasm and review

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Abstract Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, highly aggressive hematopoietic malignancy, characterized by cutaneous and bone marrow involvement and leukemic spread. Cutaneous involvement is the most common presentation in BPDCN. At present, the diagnosis and management of BPDCN are still challenging. Due to its rarity, the pediatric experience with BPDCN is especially limited. Herein, we report a special case of BPDCN with diffuse nodular lung metastases and a cutaneous lesion, which achieved a dramatic response to non-Hodgkin lymphoma regimen and remained with complete remission for 2 years. To date, acute lymphoblastic leukemia (ALL)-type chemotherapy followed by hematopoietic stem cell transplantation (SCT) is commonly thought to be related to a favorable outcome in adults with BPDCN. In contrast to it, ALL or non-Hodgkin lymphoma-type therapy alone seems enough in children with BPDCN with or without cutaneous lesions. SCT should only be performed for children who relapse and achieve a second remission. For pediatric BPDCN, further study of larger numbers of cases is needed to better define prognostic factors and optimal treatment strategy, and understand the underling differences in pathogenesis between children and adults.

Keywords Blastic plasmacytoid dendritic cell neoplasm · Chemotherapy · Child · Lung metastases

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Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, highly aggressive hematopoietic malignancy, characterized by cutaneous and bone marrow involvement and leukemic spread, representing 0.7 % of primary cutaneous lymphomas [7]. It has been described as a distinct clinicopathologic entity in the last World Health Organization classification of tumors of hematopoietic and lymphoid tissues, more infrequent in children than in adults and a poor outcome [4]. Here, we report a 10-year-old girl with BPDCN, cutaneous infiltration and diffuse nodular lung metastases and review literatures to enhance the understanding of BPDCN in children.

Case report

A 10-year-old girl was referred to the orthopedic surgeon with a history of a gradually developing painless mass on her forehead for 2 months. In the beginning, the girl just presented an asymptomatic bruise-like area on her forehead, which subsequently evolved to an erythematous plaque and a violaceous indurated tumor. After no response to anti-biotic medication, she was referred to our institution. Beside mild weight loss and fatigue, she had no other complaints and no special medical history noted. On physical examination, we saw on her forehead a large, round, violaceous cutaneous lesion, surrounded by induration with a necrotic crust, measuring 5.0×4.5×1.5 cm (Fig. 1a). Mild cervical and axillary lymph nodes were bilaterally palpable. Abnormal respiratory sounds were not heard. Laboratory findings on peripheral blood cell count, β2-microglobulin, alkaline phosphatase, lactate dehydrogenase, neuron-specific enolase and major organ function tests were all within normal ranges. Cranial computed tomography (CT) scan showed a slightly high density shade localized in the soft tissue of the forehead. Chest x-ray disclosed

extensive nodular metastases in bilateral lung fields, notably in the lower lobes. Further thoracic CT scan revealed diffuse interval development of 1.5~2.7 cm (in diameter) nodules in the lungs (Fig. 1b). Multiple space-occupying lesions with rich blood supply were found in the region of the left fibular head on magnetic resonance imaging. A biopsy was performed on her forehead tumor mass. On histology, the biopsy specimen showed a pandermal infiltrate with a diffuse proliferation of monomorphic and basophilic cells with irregularly shaped nuclei. Immunohistochemically, neoplastic cells were CD4, CD56, CD123, CD7 (dim), and Gram B positive. CD3, CD5, CD20, MPO, TdT, and TIA-1 were negative (Fig. 2a–c). In situ hybridization for Epstein-Barr virus-encoded RNAs yielded negative results. Cytologic and flow cytometric evaluation of peripheral blood, bone marrow, and cerebrospinal fluid showed no neoplastic cell infiltration. Bone marrow cytogenetics did not detect chromosomal abnormalities. These findings fulfilled the requirements for the diagnosis of BPDCN as described in the WHO classification system [4]. Thereafter, she was initiated on chemotherapy according to BFM-95 Non-Hodgkin lymphoma protocol [6], with dramatic response. Her cutaneous lesion and palpable lymph nodes rapidly decreased in size after chemotherapy. On days 33 of induction, the tumor mass on her forehead was reduced to a reddish, mildly concave cutaneous residual. At the completion of induction, a lung fine-needle biopsy under CT guidance was performed and irradiation therapy was administered to the region of the left fibular head without a central nervous system prophylaxis. According to the imaging and histopathological data, the patient achieved complete remission; until now, our patient remain in complete remission for 2 years after cessation of chemotherapy with no evidence of relapse.

Discussion

BPDCN is a rapidly evolving disease that was firstly described in 1994 in a patient with cutaneous lesion, characterized by neoplasm cells expressing CD4 and CD56 [1]. Until now, approximately 200 cases have been documented in the literature. BPDCN primarily affects the elderly, with 80 % of patients presenting with cutaneous lesions and a favorable outcome in patients without cutaneous lesions [6, 8]. Currently, the accumulated materials on phenotypic, functional, and genetic studies have pointed to its originating from hematopoietic precursors with commitment to the plasmacytoid dendritic cell lineage.

The diagnosis relies on the immunophenotypic features of the malignant cells. The expression of CD4, CD56, and CD123 in the absence of lineage-specific markers of T, B, myeloid, or natural killer cells is considered necessary to confirm the diagnosis. Although clarification of the immunophenotypic features of BPDCN has improved its recognition, it still remains a diagnostic challenge. It is necessary to note that co-expression of CD4, CD56, and CD123 is not specific, because these markers can be expressed in both acute myeloid leukemia and acute lymphoblastic leukemia (ALL). Also, atypical cases lacking CD4 or CD56 have been reported before. CD123 is most commonly thought as the specific marker of BPDCN; however, 4.4 % negative rate was reported by Cota et al. [3]. The immunophenotype of BPDCN is heterogeneous because malignant cell is derived from cells in various stages of differentiation from stem cells to mature cells. Moreover, the other specific antigen markers of BPDCN include CD303, CD2AP, T cell leukemia 1, the interleukin-3 receptor-α chain, CD101 and myxovirus A protein [3].

Due to its rarity and only recent recognition as a distinct clinicopathological entity, the experience on pediatric BPDCN is especially limited, with only a few case reports and small collections of cases described in the literature [10]. To our knowledge, our patient is the first one with diffuse nodular lung metastases and cutaneous lesion in the literature. In BPDCN, cutaneous involvement was commonly considered as an unfavorable prognostic factor, but An et al. reported an opposite result [2]. Our patient, who presented with cutaneous involvement also showed favorable outcome. Until now, no standard regimen for pediatric BPDCN has been defined yet. A variety of regimens have been employed in the treatment of BPDCN, making it difficult to define an optimal protocol. ALL-type therapies have been most

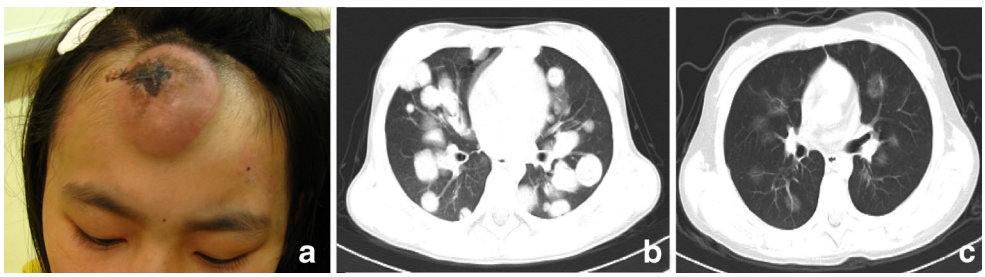

Fig. 1 **a** A large round violaceous indurated tumor with a necrotic crust on her forehead; **b** At presentation, thoracic CT scan showed diffuse nodular lung metastases; **c** At the completion of induction, thoracic CT revealed the possible lung residual disease, which was identified negative for tumor cell by fine-needle biopsy

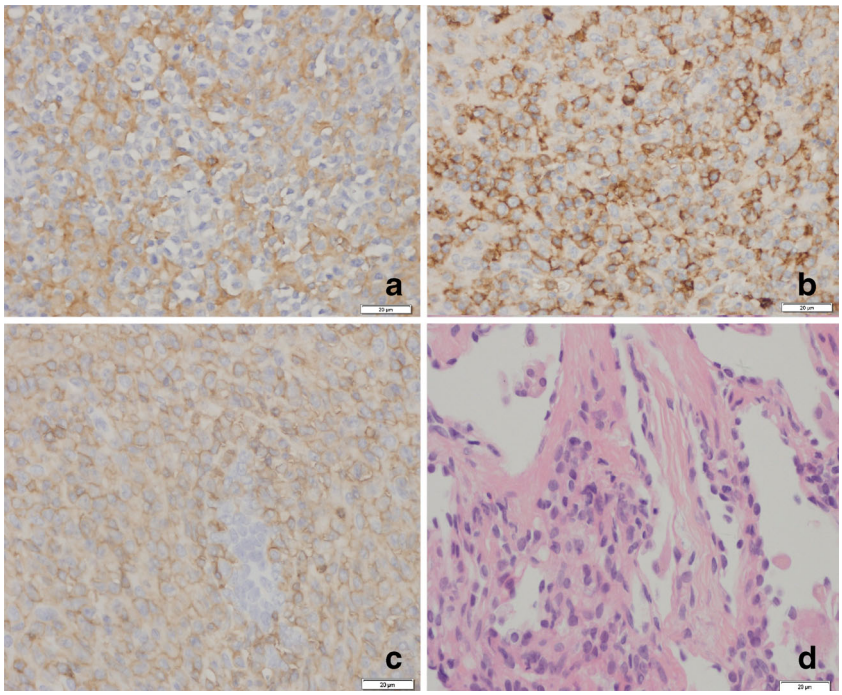

Fig. 2 Immunohistochemical staining reveals tumor cells positive for CD4, ×400 (**a**); CD56, ×400 (**b**); and CD123, ×400 (**c**). (**d**) Lung biopsy specimen showed alveolar epithelial cell proliferation, interstitial fibrosis, and dispersive infiltration of chronic inflammatory cells, and large amount of multinucleated giant cell reaction in alveolar space

commonly utilized and are associated with the best-reported results. To date, it is Reimer et al. who reported the most comprehensive retrospective study on the treatment and outcome of BPDCN, including 91 previously published cases and 6 additional patients, just four pediatric cases [9]. They found that ALL-like chemotherapy followed by allogeneic stem cell transplantation (SCT) might offer a favorable survival, with a median survival of only 13 months. In contrast to the outcome typically observed in adults with BPDCN, this disease was often associated with a relatively favorable outcome in children treated with high-risk ALL-type therapy, irrespective of SCT, and SCT did not increase the overall survival in children with BPDCN, but increased the treatment modality [5]. Non-Hodgkin lymphoma-type therapy was limited in children with BPDCN, however, it was a very successful treatment for our patient. In the largest series of pediatric BPDCN cases, six patients treated with non-Hodgkin's lymphoma-type therapy also achieved favorable outcomes [5]. Although it is generally accepted that an initial high dose of chemotherapy is essential, it still remains controversial if hematopoietic SCT should be reserved for children after the first complete remission. In contrast to the outcome of adult BPDCN, even though pediatric data on BPDCN is limited, it can also identify the difference in clinical behaviors between pediatric and adult cases.

On accumulated data, ALL/non-Hodgkin lymphoma-type therapy alone is effective in treatments of children with BPDCN with or without cutaneous lesions, SCT should only be performed for children who relapse and achieve a second remission. For pediatric BPDCN, further study on larger numbers of cases is needed to better define prognostic factors and optimal treatment strategies, as well as understanding the underling differences in pathogenesis between children and adults.

Conflicts of interest The authors indicated no potential conflicts of interest.

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