**Blastic plasmacytoid dendritic cell neoplasm with unusual extracutaneous manifestation**

Two case reports and literature review

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**Abstract**

**Rationale:** Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematologic malignancy. This disease almost always presents with cutaneous involvement.

**Patient concerns:** The 1st patient was a 16-year-old girl who presented with recurrent epistaxis. The 2nd patient was a 17-year-old female who presented with nasal obstruction and voice change for a month.

**Diagnoses:** In the 1st patient, sinonasal computed tomography (CT) revealed a 2.9-cm sized, polypoid mass in the nasal cavity. In the 2nd patient, CT scans revealed a large enhancing nasopharyngeal mass involving adenoid and several small indeterminate lymph nodes at the neck. Cutaneous examination was unremarkable for either patient. Biopsy of these 2 masses and bone marrow biopsy were performed. Histologic diagnosis of the 2 cases was BPDCN.

**Interventions:** Both patients were treated with induction chemotherapy and received allogenic peripheral blood stem-cell transplant.

**Outcomes:** No relapse was observed in the 2 patients for 14 and 11 months, respectively, after transplantation. Interestingly, they had no skin lesions at initial diagnosis or during the course of their illness.

**Lessons:** We 1st identified nasal cavity as an unusual site of BPDCN. BPDCN should be considered in differential diagnosis of blastic leukemia with an undifferentiated and ambiguous immunophenotype despite the absence of skin lesions.

**Abbreviations:** AML = acute myeloid leukemia, BPDCN = blastic plasmacytoid dendritic cell neoplasm, CT = computed tomography, WHO = World Health Organization.

**Keywords:** blastic plasmacytoid dendritic cell neoplasm, nasal cavity, skin lesion

1. **Introduction**

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematologic malignancy derived from precursors of plasmacytoid dendritic cells. This disease entity was recognized in the 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues, where it was separately included in the group of acute myeloid leukemia (AML) and related precursor neoplasm.[1] This disease almost always presents with cutaneous involvement as the 1st manifestation, with subsequent or concurrent spread to bone marrow and peripheral blood.[2-4] Although it is extremely rare, a minority but significant proportion of patients present without skin lesions. Furthermore, BPDCN present at other sites has not been yet reported. To date, nasal cavity lesion as the 1st manifestation in BPDCN has not been reported yet. Here we report 2 cases of BPDCN presenting as masses of nasal cavity and nasopharynx with leukemic manifestation without skin lesion in adolescent patients. In addition, we briefly reviewed previous cases of BPDCN without skin manifestation.

2. **Case reports**

2.1. **Case 1**

The 1st patient was a 16-year-old girl who presented with recurrent epistaxis. She had no significant medical history or family history of cancer or known genetic disorders. On sinonasal computed tomography (CT), a 2.9-cm sized, polypoid mass was noted in the nasal cavity. Cutaneous examination was unremarkable. Biopsy of this mass was performed. Histologically, the nasal mucosa diffusely expanded. It was infiltrated by atypical lymphoid infiltrates. Infiltrative tumor cells were diffuse, monomorphic medium-sized cells with fine chromatin, irregular nuclei, and scanty cytoplasm, showing blastic morphology.
Mucosal glands often became widely spaced and lost. An angiocentric and angiodestructive growth pattern were not identified. Mucosal ulceration and necrosis were not identified either (Fig. 1A, B). Immunohistochemically, atypical lymphoid cells were positive for CD2, CD4, CD56, and CD123 with focal weak staining for TCL-1, but negative for CD20, CD3, TdT, MPO, and EBV-encoded small RNA (Fig. 1C–F). No clonal TCRG or IgH gene rearrangement was detected. Peripheral blood work-up revealed pancytopenia while bone marrow biopsy revealed involvement of neoplastic cells, similar to histology and immunohistochemical findings of nasal cavity mass.

The patient was treated with induction chemotherapy with Berlin-Frankfurt-Münster regimen used for acute lymphoblastic leukemia. She achieved complete remission. After the 1st remission, she received allogenic peripheral blood stem-cell transplant (PBSCT). No relapse was observed at 14 months after transplantation. Interestingly, she had no skin lesions at initial diagnosis or during the course of their illness.

2.2. Case 2
The 2nd patient was a previous healthy 17-year-old female who presented with nasal obstruction and voice change for a month. CT scans revealed a large enhancing nasopharyngeal mass involving adenoid and several small indeterminate lymph nodes at the neck. Biopsy of the nasopharyngeal mass was performed. Microscopically, the nasopharyngeal mucosa was entirely replaced by diffuse atypical lymphoid cells with blastoid morphology (Fig. 2A, B). Immunohistochemically, these atypical lymphoid cells were positive for CD4, weak CD56, CD123, TCL1, and TdT, but negative for CD20, CD3, CD8, and CD1a (Fig. 2C–F). Peripheral blood count results were as follows: WBC, 4890/μL; Hb, 11 g/dL; and platelet, 127/μL. Blast was measured 13% of WBCs. Bone marrow biopsy showed infiltration of blastic tumor cells and demonstrated increase of CD4+, CD56+, TdT+, CD10−, and CD34− blasts up to 95% of total nucleated cells. Abdominal scan revealed mild hepatosplenomegaly while PET scan suggested hypermetabolism at nasopharynx, systemic lymph nodes, breast, liver, spleen, and bone marrow. Based on these findings, the diagnosis was most consistent with BPDCN for the 2 cases.

The patient was treated with AraC/Idarubicin (AId) induction chemotherapy. However, persistent blasts (32.5% of total nucleated cells) were observed in bone marrow biopsy. She is now taking Cladribin/Ara-C/G-CSF (CLAG) reinduction chemotherapy. After the remission, she received allogenic PBSCT. No relapse was observed at 11 months after transplantation. Interestingly, she also had no skin lesions at initial diagnosis or during the course of their illness.

3. Discussion
In this study, we report 2 cases of BPDCN in adolescent patients who had unusual extracutaneous manifestation without skin lesion. Clinicopathologically, the differential diagnosis of our cases included extranodal NK/T-cell lymphoma, acute leukemia of ambiguous lineage, and NK lymphoblastic leukemia/lymphoma. Nasal cavity lesion as the 1st clinical manifestation and CD56-positive tumor cells raised the possibility of extranodal NK/T-cell lymphoma. However, absence of angioinvasion, no
expression of cytoplasmic CD3, and cytotoxic granule proteins such as granzyme B and no association with EBV ruled out the diagnosis of extranodal NK/T-cell lymphoma. According to the 2017 WHO criteria, tumors that express some immunophenotypic features of BPDCN but not all immunohistochemical markers may be better classified as “acute leukemia of ambiguous lineage.”[5] At present, NK lymphoblastic leukemia/lymphoma is considered a provisional entity. It should be diagnosed after ruling out BPDCN. Blastic cells expressing CD56 and CD2 raised the possibility of NK lymphoblastic leukemia/lymphoma. However, CD4 positivity made it doubtful for such diagnosis. In such cases, immunohistochemical analysis including the most characteristic and reliable marker is essential for the diagnosis of BPDCN. BPDCN was initially characterized by the expression of CD4, CD56, and the lack of B cells, T cells, myeloid or monocytic cells, and NK cell markers. More specific plasmacytoid dendritic cell markers (CD123, CD303, and TCL1) have been recently used to diagnose BPDCN.[6,7] Since they are concomitantly expressed in only 46% of patients, it has been proposed that diagnosis of BPDCN can be made when 4 of these 5 markers (CD4, CD56, CD123, CD303, and TCL1) are expressed.[8] Although tumor cells of the 1st case showed focal positive for TCL1, both of 2 cases showed all 5 markers except CD303 which was not performed in our institution. Therefore, our 2 cases were histologically diagnosed with BPDCN.

The BPDCN without cutaneous lesion is exceedingly rare to diagnose. Patients without cutaneous involvement have been described in the literature. Table 1 presents a summary of 39 published cases of BPDN without skin involvement. Bone marrow involvement was observed in the majority of patients at diagnosis. Through hematopathology consultation service at the National Institutes of Health, Jegalian et al[9] have evaluated 55 BPDCN cases. Among them, 9 (16%) patients lacked cutaneous disease at presentation. A retrospective multicenter study of 43 patients (the GIMEMA study) presenting with leukemic manifestation was reported in 2012.[14] Among 43 patients, 8 (19%) cases had no cutaneous manifestations.[14] In these patients lacking skin involvement, other extracutaneous and extramedullary sites in lymph node, spleen, and liver are most commonly observed. Rauh et al[13] have demonstrated that patients with BPDCN without skin involvement and leukemic presentation show adverse prognosis than those with skin involvement. Interestingly, no case of BPDCN presenting with nasal cavity mass has been reported. It is of note that we identified nasal cavity as the unusual site of BPDCN.

Lack of traditional lineage-specific markers for B cells, T cells, myeloid, or monocytic cells with the absence of cutaneous manifestation has diagnostic challenge. The diagnosis of BPDCN is usually suspected in patients with skin lesion. Despite the absence of skin lesions and tumor involvement of unusual site, the diagnosis of BPDCN should not be ruled out since a minority of cases present with leukemia without skin involvement. Accurate recognition of BPDCN is important because of its different clinical course and outcome as well as treatment strategy compared to other differential diagnoses. In this regard, our 2 cases are significant as they have unusual presentation with leukemia in the absence of characteristic cutaneous manifestations.
4. Conclusion

In conclusion, our 2 cases demonstrate an atypical presentation without skin manifestation, characteristic of BPDCN. Although BPDCN without skin lesion is extremely rare, it should be considered in the differential diagnosis of blastic leukemia with an undifferentiated and ambiguous immunophenotype.

Author contributions

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