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Case report 1

Diagnostic challenge in a case of blastic plasmacytoid dendritic cell neoplasm; a rare entity

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Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, clinically aggressive haematological malignancy. Though the criteria for diagnosis is well defined by a set of characteristic features including clinical presentation, morphology and immunophenotype, the rarity of the disease, lack of awareness, heterogenous initial clinical presentation and lack of recurrent specific chromosomal abnormalities, make early diagnosis difficult. A high index of suspicion in appropriate cases is useful in arriving at the correct diagnosis. In young patients, intensive chemotherapy followed by consolidation with allogenic haematopoietic stem cell transplantation is considered the most effective treatment strategy. Recently, targeted therapies have shown promising results.

Introduction

BPDCN is a rare, clinically aggressive haematological malignancy derived from precursors of plasmacytoid dendritic cells. Though it can occur at any age, most patients are elderly men[1]. It commonly involves the skin (64-100%), followed by bone marrow and peripheral blood (60-90%), and lymph nodes (40-50%)[1]. Leukemic presentation without skin involvement is seen in some patients.

An accurate diagnosis of this rare disease is essential to provide appropriate treatment. BPDCN can be suspected from a set of converging features from clinical presentation to morphology. Tumour cells are monomorphic intermediate sized blasts with finely dispersed chromatin and distinct nucleoli. Blast cells with microvacuoles along the cell membrane and pseudopod-like extensions are seen. Final diagnosis relies on immunophenotyping, which is characterized by tumour cell co-expression of CD4 and CD56, as well as expression of markers more restricted to plasmacytoid dendritic cells, such as BDCA2, CD123 and TCL1 without other lineage specific markers. Recurrent specific chromosomal abnormalities are lacking.

Currently, there is no consensus regarding the best therapeutic approach. Conventional therapy includes chemotherapy and haematopoietic stem cell transplantation (HSCT). Novel therapies for BPDCN include tagraxofusp (fusion protein consisting of interleukin-3 coupled to diphtheria toxin), CD123 monoclonal antibodies, and anti-CD-123 chimeric antigen receptor T cell Immunochemotherapy (CAR-T)[2].

Here, we describe a young woman whose clinical presentation resembled acute leukaemia. Based on the morphology and immunophenotype, BPDCN was suspected. With few available additional antibodies (CD4, CD56 and CD123) together with late cutaneous involvement, the diagnosis was confirmed. Although the patient has

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an initial presentation in the blood and bone marrow, timely diagnosis of BPDCN was made due to a high index of suspicion. Early accurate diagnosis is essential to initiate prompt treatment for this aggressive disease.

This case report follows the CARE Guidelines.

Case report

A 30-year-old previously healthy woman presented to the local hospital with a two weeks history of fever and sore throat. Complete blood count and blood film morphology (Figure 1) revealed severe cytopenia with circulating blasts. Physical examination was insignificant apart from pallor and enlarged tonsils. She was transferred to a tertiary care hospital with a preliminary diagnosis of acute leukemia. Imaging studies revealed mild hepatosplenomegaly and bilateral cervical and axillary lymphadenopathy (sub centimeter in size). Other investigations showed very high inflammatory markers including serum ferritin. Liver function was slightly abnormal with preserved renal function. Coagulation screen and uric acid were within normal range. While further investigations were carried out to reach an accurate diagnosis, optimal supportive care was provided. Bone marrow trephine biopsy (Figure 2) and flow cytometry from peripheral blood were performed. Morphologically, the neoplastic cells were intermediate sized blasts with finely dispersed chromatin and distinct nucleoli. Some blastic cells showed pseudopod-like cytoplasmic extensions. Flow cytometry of the peripheral blood revealed a population of abnormal cells, which did not detect myeloid/B/T/NK lineage specific markers or CD34/TdT. Abnormal cells expressed CD4, CD56, CD123 and HLA DR (Figure 3).

Based on the morphology and immunophenotyping the diagnosis of BPDCN was made. Though initially she did not have any cutaneous manifestations, on day 5 of her hospital admission, she developed multiple small nodular lesions close to the corner of her mouth with rapid progression to ulceration and hyperpigmentation.

The patient was informed of the diagnosis. The prognosis, available treatment modalities, and the haemato-oncology units with various levels of facilities were discussed in detail and adequate time was given for her and her family to make their choice. The patient was transferred to a haemato-oncology unit with facilities for allogenic haematopoietic stem cell transplantation for further management.

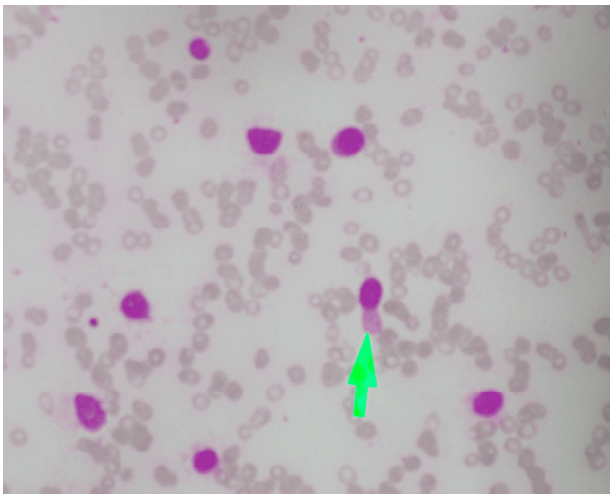

Figure 1. Peripheral blood film showing circulating blasts.

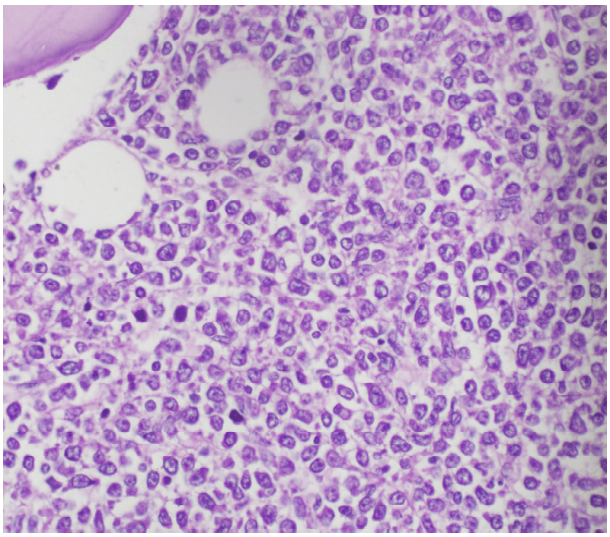

Figure 2. Trephine biopsy.

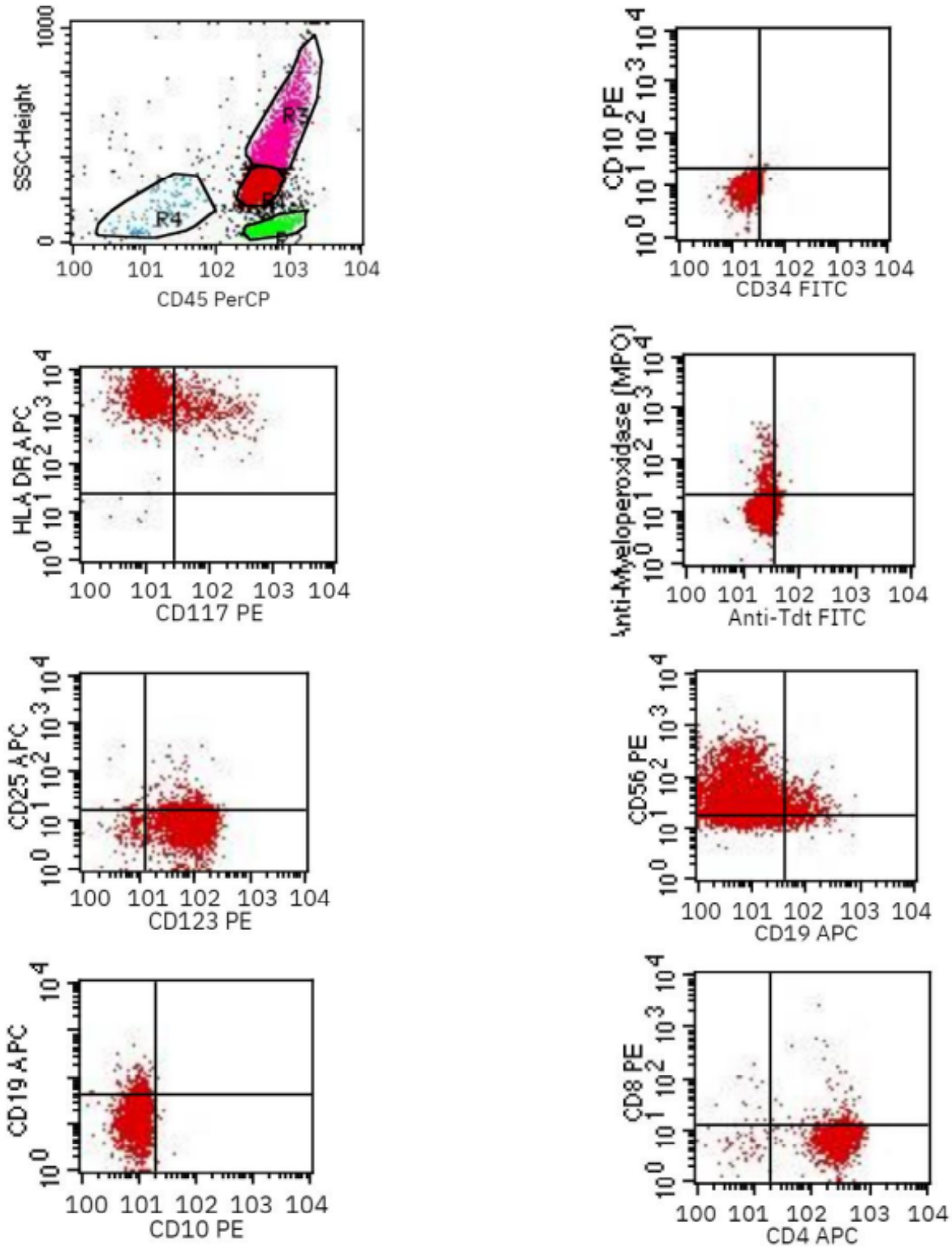

Figure 3. Flow cytometry from peripheral blood.

Discussion

Due to its rarity, recent inclusion in the WHO classification as a separate entity, and lack of awareness, there is a possibility to misdiagnose BPDCN. Our patient presented with leukaemic dissemination without cutaneous involvement at the onset. Most patients with BPDCN are elderly with the median age at diagnosis of 61-67 years[1]. Male to female ratio is 3.3:1[1]. However, the morphology and initial immunophenotypic profile were not in keeping with acute leukaemia and triggered suspicion of alternative diagnoses. Due to significant resource limitations, inclusion of multiple immunophenotypic markers was not possible at our institution. Expert opinion was obtained via telemedicine before further work-up. The diagnosis was narrowed to BPDCN and acute leukaemia with monocytic differentiation. An additional panel of markers consisting of CD14, CD11b, CD4, CD56 and CD123 was performed and offered additional support for the diagnosis. Subsequently, the patient developed skin involvement, which reinforced the diagnosis. The unavailability of highly specific markers such as CD303 (BDCA2), CD304, TCL1, and TCF4 in our laboratory is a limitation. Lack of recurrent specific chromosomal abnormalities in this disease entity is another drawback. High index of suspicion helped in arriving at the correct diagnosis.

The clinical course of BPDCN is aggressive with a median survival of 10.0 to 19.8 months[1]. In young patients, intensive chemotherapy followed by allogeneic HSCT has been recommended as the best way to achieve long-term survival[1]. A multicentre retrospective study conducted in the United States and Canada showed allogenic HSCT in first complete remission yielded superior 3-year overall survival[3]. However, the best treatment for elderly patients is yet to be established.

The need for novel targeted agents for treatment of this aggressive disease was well recognized. Knowledge on the pathophysiology of disease is essential for designing innovative therapeutic strategies. Based on karyotyping, gene expression profiling and next generation sequencing the main biological players seems to be the epigenetic regulation, activation of the NF-kB pathway and resistance to apoptosis[4].

Tagraxofusp is widely becoming a standard first line treatment in the United States. In an open label multicohort study in adult patients with untreated or relapsed BPDCN, the use of tagraxofusp led to clinical response[5].

Due to high CD123 expression, BPDCN can be targeted by anti-CD123 CAR-T therapy and CD123 monoclonal antibodies with success[2]. These novel therapies are not yet available in Sri Lanka. Considering her age, chemotherapy followed by allogeneic HSCT was considered the best treatment option.

Conclusion

BPDCN is a rare clinically aggressive haematological malignancy. Accurate early diagnosis is essential for prompt treatment. Leukaemic presentation of BPDCN with late cutaneous involvement in a young woman is uncommon. Unavailability of highly specific immunophenotype markers due to resource limitations and lack of recurrent specific chromosomal abnormalities in this rare entity are additional limitations. High index of suspicion based on morphology and available immunophenotype findings together with timely input of expert opinion helped in arriving at the correct diagnosis.

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