Blastic plasmacytoid dendritic cell neoplasm - immunophenotype CD56 negative

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Summary

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare haematological malignancy of dendritic cell precursors. The present study describes a case of BPDCN occurring in a 74-year-old female with only cutaneous lesions at first presentation. Diagnosis was challenging and initially eluded physicians as histopathology favoured a reactive process. After disease progression and repeated investigations, a diagnosis of BPDCN was reached, although uncharacteristically the specific immunophenotype CD56 remained negative. The present study emphasises the importance of dermatologists and pathologists being aware of this uncommon disease in order to avoid misdiagnosis and to initiate early appropriate management.

KEY WORDS: blastic plasmacytoid dendritic cell neoplasm (BPDCN); haematological malignancy; immunophenotype; CD56.

Introduction

BPDCN is a rare subtype of leukemia/lymphoma and as such it is classified under the 2008 World Health Organisation acute myeloid leukemia (AML) and related precursor neoplasms (1). It is an aggressive and rare hematological malignancy, representing less than 1% of all acute hematological malignancies. BPDCN was previously known as various descriptive names, including agranular CD4+ natural killer (NK) cell leukemia, blastic NK cell lymphoma/leukemia and CD4+ CD56+ hematodermic neoplasm/tumor (2). Approximately 300 cases of this disease have been reported worldwide, with 100 cases being reported in the last decade (2-4). BPDCN is mainly a disease of the elderly, with a median age of onset between 60 and 70 years, although rare cases have been reported in children. The male to female ratio is approximately 3:1, with no ethnic or geographic predilection (2, 5). Much has been learned about this disease since its discovery in the mid 1990s, however the pathogenesis remains unclear and there has been no increase in median survival being 12 to 14 months (6). The cutaneous manifestations of BPDCN are asymptomatic, violaceous, dermal lesions that present as nodules or bruise-like infiltrates (7). This represents the invasion of plasmacytoid dendritic cells into the dermis as seen on histology from a skin biopsy. In the majority of cases, BPDCN presents with extracutaneous manifestations, such as regional lymphadenopathy and involvement of the bone marrow. However, these manifestations are rarely seen without cutaneous involvement (3). A retrospective study of 90 BPDCN patients who had disseminated cutaneous findings also had extracutaneous involvement (8).

Case report

A 74-year-old female presented with an asymptomatic, violaceous rash over her forehead that had been present for two weeks (Figure 1 a and b). Full skin examination also revealed a similar nodule on her back (Figure 1 c). There was no associated lymphadenopathy. She had been feeling well with no constitutional symptoms. The patient had a previous history of diffuse large B-cell lymphoma (DLBCL), which was diagnosed following a pathological femoral fracture 8 years earlier. She underwent surgical fixation of her femur and received 8 cycles of rituximab-cyclophosphamide/hydroxydaunomycin/vincristine/prednisolone (R-CHOP). She had stem cells collected but did not have an autologous stem cell transplant. She achieved complete remission and has good functional status. A skin biopsy was performed. Histology revealed atypical lymphoid infiltrate. Immunohistochemical stains were positive for CD45, CD20, CD3, CD5, CD68 and bcl2 and negative for CD43, CD79A, CD21, bcl6, CD10, Kappa and Lambda and MPO. Direct immunofluorescence was unremarkable and the overall opinion from the pathologist was that this was consistent with reactive changes. Routine laboratory tests were within normal ranges. Due to the patient’s history of DLBCL her haematolo-
gist performed peripheral blood flow cytometry and a bone marrow aspiration that revealed no evidence of tumor cells. Additionally, a positron emission tomography (PET) scan revealed solitary uptake of an inguinal lymph node, which was subsequently biopsied and also consistent with reactive changes. Her condition progressed in the subsequent 3 months (Figure 2), however she remained well and asymptomatic.

Figure 1 - a) and b) Subtle bruise-like rash on both cheeks, forehead and glabella region. c) Bruise like nodule back.

Figure 2 - Disease progression noted cutaneous only: a) 2 weeks post presentation; b) approximately 1 month post presentation back; c) face and d) back just over 3 months post presentation.
Skin biopsy was performed again. Histology showed a deep atypical lymphocytic infiltrate (Figure 3 a and b). Immunohistochemical stains were positive for CD43, CD4 and TdT (Figure 4 a, b and c) and negative for CD56 as well as the lineage-specific markers for B cells, T cells, myeloid cells and monocytes. Her platelets decreased from 230 down to 130 and her peripheral blood flow cytometry was abnormal and revealed CD56 cells. Her repeat bone marrow aspiration revealed 69% involvement and a PET scan showed no internal involvement. The diagnosis of BPDCN was reached and she underwent hyperfractionated cyclophosphamide/vincristine/doxorubicin/dexamethasone (HyperCVAD) at Nambour General Hospital and currently remains in remission 14 months post diagnosis.

Discussion

BPDCN is diagnosed with a biopsy showing a diffuse, monomorphic infiltrate of atypical lymphocytes with scant, agranular cytoplasm with varying number of mitoses. Epidermotropism, angioinvasion and coagulative necrosis are absent (1). The demonstration of specific immunophenotypes either by immunohistochemistry and/or flow cytometry confirms the phenotype CD4, CD56, and/or CD123 (2, 5).

This case highlights the clinical progression of BPDCN as rapid and aggressive. In the initial stage of her disease, the cutaneous findings were obvious even though extensive investigations did not reveal the diagnosis. One possible cause for this is that the immunophenotype of BPDCN overlaps with the immunophenotype occurring in reactive lymph nodes, except for the expression of CD56 and terminal deoxynucleotidyl transferase (TdT) (1, 9). TdT expression was positive in this case as it is in approximately one third of cases, but the unique aspect of the case was that the blastic marker for CD56 was negative. Rarely this has been reported (10). BPDCN diagnosis can be difficult to achieve due to its clinical and biological heterogeneity, as well as its overlapping features with other hematologic malignancies.

When CD56 is positive, differential diagnoses such as myeloid sarcoma and extranodal NK/T cell lymphoma need to be excluded with a more extensive immunohistochemical panel (11, 12). Immunohistochemical stains for lineage-specific markers for B cells (CD20, CD19, CD79a), T cells (CD3, CD5), myeloid cells (myeloperoxidase) and monocytes (CD11c, CD163, lysozyme) should be negative.

A recent study by Sangle et al. suggested that positive staining for CD56, TdT, or TCL1 and negative results

![Figure 3 - Haemotoxolin and eosin stain of a punch biopsy; a) x 40 dense, diffuse, monomorphic infiltrate of lymphocytes with no epidermotropism; b) x 400 atypical lymphocytes with scant, agranular cytoplasm with varying number of mitoses. No angioinvasion or coagulative necrosis.](image)

![Figure 4 - Immunohistochemical staining at 200x magnification: a) CD4 positive stain; b) CD43 positive stain; c) Terminal deoxynucleotidyl transferase (TdT) positive stain.](image)
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for lysozyme and myeloperoxidase is the most reliable immunophenotype to diagnose BPDCN (12). The etiology remains unknown for BPDCN. Pagano et al. observed 43 patients with BPDCN and found 6 patients who had received chemotherapy for a previous malignancy. This correlation is similar to our patient, who had received previous chemotherapy for DLBCL 8 years earlier. Pagano et al. observed a median time of latency between chemotherapy exposure and the diagnosis of BPDCN to be 5 years (7). Prognosis for patients with BPDCN is poor with a reported overall survival rate of 12 to 14 months. There is no consensus on the most appropriate treatment for BPDCN. While responding well to aggressive chemotherapy regimes, it tends to inevitably relapse and return as a more resistant disease, heralding a poor prognosis (4). A promising therapeutic modality is hematopoietic stem cell transplant in patients who achieve their first complete remission with chemotherapy, however a randomised control trial establishing standard frontline treatment regimens do not exist. A better understanding of disease pathophysiology could, in the near future, help identify markers for targeted therapy as well as improve prognostic tools.

Conclusion

BPDCN is a rare neoplasm of dendritic cell origin that often presents at an advanced stage with cutaneous infiltration and bone marrow involvement. As illustrated in this case, a possible reason for the advanced disease at diagnosis is partly due to rapid progression of the disease itself but also difficulty with diagnosing early stage BPDCN. The majority of cases of BPDCN has cutaneous involvement, suggesting that clinical suspicion amongst dermatologists should be high with new, bruise-like, infiltrative lesions in an elderly patient, especially if they are known to have a history of chemotherapy. Although the diagnosis of BPDCN is made pathologically, this case illustrates the difficulty in early diagnosis and emphasises that re-biopsying lesions is sometimes necessary to establish the correct diagnosis.

References