CASE REPORT

Blastic plasmacytoid dendritic cell neoplasm (BPDCN): a rare entity

Ming Sheng Lim,¹ Karla Lemmert,² Anoop Enjeti¹

¹Department of Haematology, Calvary Mater Newcastle, Waratah, New South Wales, Australia

²Department of Flow Cytometry, Pathology North Hunter, NSW Pathology, Newcastle, New South Wales, Australia

Correspondence to

Dr Ming Sheng Lim, limmingsheng@hotmail.com

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SUMMARY

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive haematological malignancy in the elderly, with a high frequency of cutaneous and bone marrow involvement and poor prognosis. We report a case of BPDCN with classic presentation and discuss its treatment and the value of different investigation tools used in diagnosis and response assessment.

BACKGROUND

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive haematological malignancy derived from precursor plasmacytoid dendritic cells, predominantly affecting the elderly, with a high frequency of cutaneous and bone marrow involvement, leukaemic dissemination and a poor prognosis. Limited data exist regarding its exact incidence but it is estimated to account for 0.44% of all haematological malignancies,¹ less than 1% of acute leukaemias² and 0.7% of cutaneous lymphoma.³ It was first described in 1994 as a CD4 positive CD56 positive cutaneous lymphoma.⁴ Over the past 20 years, its nomenclature has evolved, and various terms have been used to describe this entity including blastic natural killer cell lymphoma/leukaemia,⁵ agranular CD4+ natural killer cell leukaemia⁶ and agranular CD4+ CD56+haematodermic neoplasm.⁷ It is currently classified under acute myeloid leukaemia (AML) and related precursor neoplasms in the 2008 WHO classification of tumours of haematopoietic and lymphoid organs.⁸ Despite this, it was not until recently that the origin of BPDCN was confirmed at a molecular level to be of myeloid lineage and to arise from resting plasmacytoid dendritic cells. Furthermore, the molecular profile was not shown to be clearly associated with either acute myeloid (AML) or lymphoid leukaemia (ALL), but had a distinct profile intermediate between the two.⁹

CASE PRESENTATION

A 75-year-old man presented with a 3-week history of nodular violaceous rash over his forehead, forearms, chest and back (figure 1A–C). His history included radical prostatectomy for prostate cancer, hypertension, hyperlipidaemia and type 2 diabetes. He was otherwise well and denied any B symptoms. Examination revealed multiple 2–3 cm nodular, violaceous nodules and plaques over his forehead, chest, back and forearms. There was no palpable lymphadenopathy or hepatosplenomegaly.

INVESTIGATIONS

Skin biopsy from his chest revealed an extensive and slightly patchy dermal infiltrate, without epidermotrophism, consisting of uniform cells with oval-shaped nuclei, fine chromatin and inconspicuous cytoplasm (figure 2A, B). On immunostaining, the tumour cells were positive for CD4, CD56 and CD43 and negative for CD3, CD20, CD30, ALK1, CD8, EBER, perforin, myeloperoxidase and CD15.

Figure 1 (A) Photograph showing multiple bruise-like or violaceous nodules and plaques on the (A) trunk and (B) face. (B) Photograph showing multiple bruise-like or violaceous nodules and plaques on the (A) trunk and (B) face. (C) Close-up view of the bruise-like plaques on the trunk.

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Figure 2 (A) Skin biopsy from the chest. (A) An extensive slightly patchy dermal infiltrate without epidermotropism (H&E, $\times 40$). (B) Skin biopsy from the chest. (B) High power view showing uniform cells with oval-shaped nuclei, fine chromatin and inconspicuous cytoplasm. (H&E, $\times 400$).

Complete blood count showed mild normochromic normocytic anaemia and the presence of circulating blasts. The bone marrow aspirate and trephine biopsy showed infiltration with 90% blasts (figure 3A, B). Flow cytometry demonstrated an abnormal blast population with immunophenotyping similar to peripheral blood. This population was positive for CD45 (dim), CD4, human leucocyte antigen (HLA)-DR, CD56, CD38+ and CD123 bright (figure 4A–E). The population was negative for lineage markers including MPO, CD79a (figure 4F), cytoplasmic CD3 and myeloid markers CD13, CD33, CD64 and CD14 (not shown). A diagnosis of BPDCN was made on the basis of clinical, morphological and immunophenotypic characteristics.

Cytogenetic analysis revealed multiple abnormalities including add (1), del 4q and 5q, -15 and -17 , $+16$ in 9/20 metaphases. Fluorescence in situ hybridisation (FISH) demonstrated loss of ABL1 (Abelson murine leukaemia viral oncogene homolog 1) (9q34.1). positron emission tomography CT for staging showed fluorodeoxyglucose avid malignancy in the spleen, lymph nodes including the mediastinum as well as confirmed uptake in subcutaneous lesions on the torso and skull.

DIFFERENTIAL DIAGNOSIS

Diagnosis of BPDCN is based on clinical, morphological, immunophenotypic, cytogenetic and molecular features. The differential diagnosis includes mature T-cell lymphoma, nasal-type NK/T-cell lymphoma, myeloid sarcoma/acute myeloid leukaemia and T-cell lymphoblastic lymphoma/leukaemia.

Figure 3 (A) Preinduction bone marrow aspirate and trephine biopsy. Aspirate (A) showing a heterogeneous population of small to medium-sized cells with oval or irregular nuclei, fine chromatin, prominent nucleoli and scant to moderate basophilic agranular cytoplasm. (H&E, $\times 400$). (B) Preinduction bone marrow aspirate and trephine biopsy. (B) Trephine showing a hypercellular marrow with extensive infiltration by a heterogeneous population of primitive cells. (H&E staining, $\times 400$).

TREATMENT

Owing to his age and comorbidities, the patient was started on induction chemotherapy using a modified acute lymphoblastic leukaemia protocol consisting of vincristine, prednisone and daunorubicin.¹⁰

OUTCOME AND FOLLOW-UP

The patient tolerated the chemotherapy well apart from steroid-induced hyperglycaemia and had an excellent response with complete resolution of his skin lesions by day 15. He had neutropenia which responded well to filgrastim (G-CSF) but did not require any transfusion support with red cells or platelets. A repeat bone marrow biopsy performed on day 34 revealed a significant reduction in blast count (figure 5A, B) with 9% residual blasts detected by flow cytometry and demonstrated by trephine immunohistochemistry (figure 5C). In view of the findings on repeat marrow biopsy, the patient has been started on cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (oncovin) and prednisone (CHOP) and is still undergoing treatment. This regimen was chosen with palliative intent over other potentially more effective therapies in view of the patient's age, comorbidities, rural location, social isolation and

Figure 4 (A) Flow cytometric analysis of a bone marrow aspirate sample at diagnosis. The abnormal blast population is positive for (A) CD45 (dim), (B) CD4++, (C) HLA-Dr++, CD56++, (D) CD38+, (E) CD123+-. This population is negative for lineage markers including (F) MPO, CD79a, cytoplasmic CD3 and myeloid markers CD13, CD33, CD64 and CD14 (not shown).

preference to have ongoing treatment requiring minimal monitoring and closer to home.

DISCUSSION

This case illustrates a classic presentation of BPDCN. The median age of diagnosis is 68,¹¹ although it has been reported to occur in patients under the age of 50 years in up to 30% of cases¹² and can occur in children.¹³ Male to female ratio is 3:1.¹² The majority (up to 90%) of patients present with asymptomatic skin lesions, although rare cases present in the leukaemic phase without cutaneous involvement.^{11 14 15} Skin lesions may be solitary or multiple, ranging from nodules to patch plaques or bruise-like areas which may be associated with erythema, hyperpigmentation, purpura and ulceration.¹² Extra-cutaneous disease is common, including regional lymphadenopathy (56%), splenomegaly (44%) and hepatomegaly (42%).¹¹ Peripheral blood and bone marrow involvement is variable and occurs in 60–90% of patients at diagnosis. Cytopenias are common, with thrombocytopenia (78%) being the most common, followed by anaemia (65%) and neutropenia (34%).¹⁶

Flow cytometry/immunohistochemistry is essential to differentiate BPDCN from other haematological malignancies which can also present with cutaneous and bone marrow involvement including mature T-cell lymphoma, nasal-type NK/T-cell lymphoma, myeloid sarcoma/AML, and T-cell lymphoblastic lymphoma/leukaemia. However, it is also important to note that acute myeloid/myelomonocytic leukaemia and myelodysplastic syndrome may be present before or at diagnosis and develops subsequently at progression or relapse in 10–20% of cases.^{17–19} BPDCN cells can be identified by low CD45/side scatter within the blast cluster blast cluster which typically express CD4,

CD56, HLA-DR and are CD123 (IL-3R α chain) bright consistent with their proposed plasmacytoid dendritic cell (pDC) origin. They are negative or dim for lineage markers expressed by myelomonocytic cells (CD64, CD14, lysozyme and MPO) and lymphoid cells (CD19, CD3, cCD3 and cCD79a).^{7 16 20 21}

Karyotypic abnormalities are found in about two-thirds of patients and are usually complex with no specific single chromosomal aberrations. Six major recurrent chromosomal abnormalities have been reported, involving chromosomes 5q (72%), 12p and 13q (64%), 6q (50%), 15q (43%) and 9 (28%).¹⁹ Cytogenetic abnormalities in our patient, not previously reported, include abnormalities of chromosomes 4, 16 and 17.

Molecular studies including gene expression profiling and whole exome sequencing/target sequencing have led to the identification of upregulated pathways, for example, nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B)⁹ and common somatic mutations (TET2 (36%), ASXL1 (32%), NPM1 (20%), NRAS (20%), IKZF1 (20%), IKZF1–3 (20%), ZEB2 (16%), HOXB9 (4%) and UBE2G2 (4%)).²² The use of next generation sequencing has confirmed the high frequency of TET2 mutations and identified novel mutations such as ZRSR2.^{23 24} Most of these mutations involve DNA methylation (TET2), chromatin modification (ASXL1) or splicing factor genes (ZRSR2).

There is currently no consensus regarding optimal treatment for this rare entity as prospective data are lacking. The prognosis regardless of type of therapy has generally been disappointing with overall survival of 12–16 months and high rate of relapse within 9–11 months. However, patients with disease limited to the skin and with single lesion presentation may have a better prognosis, and these patients may benefit

Figure 5 (A) Postinduction bone marrow aspirate and trephine biopsy. (A and B) Significant reduction in blast percentage on bone marrow aspirate and trephine. (H&E, $\times 400$). (B) Postinduction bone marrow aspirate and trephine biopsy. (A and B) Significant reduction in blast percentage on bone marrow aspirate and trephine. (H&E, $\times 400$). (C) Postinduction bone marrow aspirate and trephine biopsy. (C) Immunostaining for CD123 reveals residual clusters of CD123 cells corresponding to the malignant blast cells seen on H&E ($\times 400$).

from radiotherapy alone.²⁵ In most studies, polychemotherapy was used including ALL-type therapy, AML-type therapy and lymphoma type therapy. ALL type treatment has produced better results than AML type therapy in terms of survival outcomes and complete remission rates based on retrospective data.^{11 20} CHOP or CHOP-like regimens have

had variable results with complete remission rates of 55–80%.^{20 26} However, the relapse-free survival is short (mean 5 months).²⁷ Long-term overall survival has been achieved in patients treated with allogeneic transplant or autologous transplant in first complete remission (CR).^{11 28} Nevertheless, from a practical point of view, this may not be feasible due to advanced age at presentation. SL-401 is a recombinant fusion protein composed of diphtheria toxin fused to IL3 which binds to the IL3 receptor (CD123) highly expressed on BPCDN cells. A prospective phase 1/2 study of 11 patients who received a single course of SL-401 was promising.²⁹ If successful, the use of SL-401 and other targeted therapies such as lorvotuzumab mertansine, a CD56 drug antibody conjugate (in ongoing phase 2 clinical trials, ClinicalTrials.gov Identifier: NCT02420873), are an attractive option in this group of patients with advanced age to improve therapeutic efficacy while minimising toxicity. Participation in clinical trials is therefore highly recommended.

A repeat bone marrow biopsy performed at day 34 showed that blasts were detectable by immunohistochemistry and by flow cytometry with immunophenotype similar to the original diagnosis. The definition of CR has not been well documented in previous case reports, and indeed it is unclear whether a bone marrow biopsy was performed after induction chemotherapy to determine remission status. Although anecdotal, this suggests that bone marrow biopsy, including flow cytometry and/or immunohistochemistry, should be considered in patients postinduction chemotherapy to assess remission status even if cutaneous manifestations have resolved.

In conclusion, since BPCDN is a rare condition with an aggressive course and a poor prognosis, it is important to recognise it. Flow cytometry and/or immunohistochemistry are essential for making a diagnosis of BPCDN and distinguishing this from other haematological malignancies. It may also be useful to assess remission status with flow cytometry, FISH or a chromosomal marker, especially if the morphological blast count is low.

Learning points

- ▶ Blastic plasmacytoid dendritic cell neoplasm (BPCDN) is a rare condition of the elderly with cutaneous and bone marrow manifestations.
- ▶ It has an aggressive course and a poor prognosis.
- ▶ No optimal treatment exists, with a high relapse rate regardless of therapy used.
- ▶ Flow cytometry and/or immunohistochemistry are essential for making a diagnosis of BPCDN and distinguishing this from other haematological malignancies. It may also be useful to assess remission status with flow cytometry, fluorescence in situ hybridisation or a chromosomal marker, especially if the morphological blast count is low.

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Competing interests None declared.

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